I Peptide isosteric replacement preparation using zinc-mediated chain extension-aldol reactions II Formal synthesis of (+)-Brefeldin A III Zinc-mediated chain extension reactions with substituted carbenoids

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I. PEPTIDE ISOSTERIC REPLACEMENT PREPARATION USING 
ZINC-MEDIATED CHAIN EXTENSION-ALDOL REACTIONS 

II. FORMAL SYNTHESIS OF (+)-BREFELDIN A 

III. ZINC-MEDIATED CHAIN EXTENSION REACTIONS WITH 
SUBSTITUTED CARBENOIDS 

By 

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B.S., Peking University, 2000 

DISSERTATION 

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September, 2006
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DEDICATION

I wish to dedicate this dissertation to Hongchun Lin (dad), Ainv Wu (mom), and Weili Lin (brother).
ACKNOWLEDGEMENT

I would like to thank my advisor Prof. Charles K. Zercher for his inspirational instruction and guidance during my study at UNH. In addition to his excellent teaching and research, Prof. Zercher is always very patient and taught me valuable life lessons. All of which I am forever indebted to him for.

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ABSTRACT

I. PEPTIDE ISOSTERIC REPLACEMENT PREPARATION USING ZINC-MEDIATED CHAIN EXTENSION-ALDOL REACTIONS

II. FORMAL SYNTHESIS OF (+)-BREFELDIN A

III. ZINC-MEDIATED CHAIN EXTENSION REACTIONS WITH SUBSTITUTED CARBENOIDs

By

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University of New Hampshire, September, 2006

A series of amino acid derived alpha-substituted-gamma-keto amides and esters have been prepared by zinc-mediated chain extension and tandem chain extension aldol reactions with various aldehydes and ketones. An efficient diastereoselective synthetic route has been developed to approach a proposed inhibitor for HCMV (Human Cytomegalovirus) protease using this zinc-mediated tandem chain extension-aldol reaction as the key step. An asymmetric formal synthesis of (+)-Brefeldin A has been developed in which the zinc-mediated ring expansion /oxidation /elimination method constitutes a key step. Preparation of
beta-alkyl-gamma-keto esters through a chain extension reaction using substituted carbenoids has also been accomplished.
CHAPTER I

PEPTIDE ISOSTERIC REPLACEMENT PREPARATION USING
ZINC-MEDIATED CHAIN EXTENSION-ALDOL REACTIONS

1. Introduction

a) Introduction to Peptide Isostere

The understanding of enzymatic catalysis is based on the concept that the enzyme possesses a unique ability to stabilize the transition state.¹ The transition state in a peptide hydrolysis reaction will possess significant tetrahedral character, which suggests that efficient inhibitors should provide a method to mimic this tetrahedral character. The nucleophile responsible for the peptide bond 1 cleavage in the active site of a serine protease is a serine residue. Upon its nucleophilic attack, a tetrahedral intermediate 2 is formed. Collapse of the tetrahedral intermediate to form the trigonal product requires the loss of a leaving group. If this leaving group is a portion of the peptide chain, successful cleavage of the peptide bond has been accomplished. The serine protease, upon hydrolysis of the serine ester, is available for further catalysis (Scheme 1).²
One strategy for protease inhibition involves the utilization of a non-hydrolyzable peptide mimic; in other words, a mimic that can be recognized by the enzyme’s active site, but is unable to be processed (cleaved) by the enzyme. The ability to adopt a tetrahedral geometry through nucleophilic attack of the serine residue in a serine protease would be advantageous due to the expected enhanced binding in the active site; however, if the only possible leaving group of the collapsing tetrahedral intermediate is the serine residue, the inhibitor is not hydrolyzed.

The term ‘isostere’ refers to an atom or a group of atoms that are designed to mimic the steric, and to a lesser extent the electronic properties of another atom or group. Peptide isosteres are groups of atoms that are designed to mimic the peptide (amide) bond found in a peptide chain. A variety of peptide isosteres have been developed and studied, including the ketomethylene, α,α-difluoroketomethylene...
hydroxyethylene, alkene-based systems, and others (Figure 1). One advantage of the ketomethylene system, and that of the α-fluoroketones, is the ability of the ketone functionality to accept a nucleophile and adopt a tetrahedral geometry, yet maintain its resistance to hydrolytic cleavage.

The ketomethylene isostere has been studied with a variety of enzymatic systems: e.g. angiotensin-converting enzyme (ACE), HIV protease, influenza viral protease, transpeptidase enzyme, and many aspartyl and serine proteases. A variety of methods have been developed to prepare ketomethylene isosteres, many of which are described below.

The application of a Grignard reagent to peptide isostere preparation has been described frequently (Scheme 2). For example, an amino aldehyde can be reacted with a Grignard reagent derived from a three-carbon alkyl halide to generate an
alcohol intermediate. After oxidation of the alcohol, γ-keto ether 10 can be prepared. Through deprotection of the benzyl group and further oxidation, the γ-keto carboxylic acid 11 is generated and is available to couple amino acids to extend the ketomethylene-containing peptide chain. Racemization of the α-position is often observed due to the acidic property of the α-amino aldehyde.

\[
\begin{align*}
\text{CH}_3 & \text{BrMg} \quad \text{CH}_3 \\
\text{9} & \quad \text{10}
\end{align*}
\]

1) H2/Pd
2) PCC

Further coupling with amino acids

\[
\begin{align*}
\text{R'} & \text{R}
\end{align*}
\]

Peptide isostere

**Scheme 2: Peptide Isostere Preparation Using a Grignard Reagent**

Another approach to ketomethylene isostere involves using alkylation of a β-keto ester 13 as a key step to approach the γ-keto ester (Scheme 3). The β-keto ester 13 can be prepared through a modified Claisen condensation using 1,1-carbonyldiimidazole (CDI) as a carboxyl activation agent. A bromoester derivative was applied to alkylate the β-keto ester 13 using sodium hydride as a base. Upon treatment with trifluoroacetic acid (TFA), the t-butyl ester is cleaved and
decarboxylation offers the γ-keto ester 14. Ester cleavage with lithium hydroxide and amide coupling with proline methyl ester provide the peptide chain mimic.

\[
\begin{align*}
\text{CbzHN} & \quad \text{OH} \\
12 & \quad \text{a) CDI} \\
& \quad \text{b) } \text{CbzHN} \quad \text{R} \quad \text{O} \quad \text{O} \\
& \quad \text{CbzHN} \quad \text{R} \quad \text{O} \quad \text{O} \quad \text{Li} \\
& \quad \text{O} \quad \text{O} \quad \text{13} \\
\end{align*}
\]

\[
\begin{align*}
\text{NaH, BrCH}_2\text{COOEt} & \quad \text{TFA} \\
1) & \quad \text{CbzHN} \quad \text{R} \quad \text{O} \quad \text{O} \\
& \quad \text{CbzHN} \quad \text{R} \quad \text{O} \quad \text{O} \quad \text{Et} \\
2) & \quad \text{LiOH} \\
& \quad \text{R} \quad \text{O} \quad \text{O} \quad \text{Et} \\
\end{align*}
\]

\[
\begin{align*}
\text{EDC, HOBT} & \quad \text{Pyridine} \\
& \quad \text{CbzHN} \quad \text{R} \quad \text{O} \quad \text{O} \\
& \quad \text{CbzHN} \quad \text{R} \quad \text{O} \quad \text{O} \quad \text{Me} \\
& \quad \text{COOMe} \\
\end{align*}
\]

**Scheme 3:** Peptide Isostere Preparation through Alkylation of a β-Keto Ester

The modified Dakin-West reaction constitutes another approach to obtain the racemic γ-keto ester 19 (Scheme 4). A reaction between the oxazolone derivative 16 and an acyl chloride using triethylamine as a base provides oxazole derivative 17. Heating 17 with pyridine offers the migration product 18. Hydrolysis with acetic acid followed by decarboxylation led to the formation of the dipeptide ketomethylene mimic 19 with nitrogen atom functionalized with a benzoyl group.
Scheme 4: Peptide Isostere Preparation Using Modified Dakin-West Method

In 1995, Rudd's research group reported the transformation of a β-keto sulfone intermediate into a ketomethylene isostere (Scheme 5). The Boc-protected amino acid ester derivative 20 is reacted with a methylphenylsulfone dianion to form the desired β-keto sulfone 21. The sulfone is reacted with the bromoacetamide derived from an amino acid to provide the β-keto sulfone intermediate 22. A ketomethylene tripeptide isostere 23 was obtained through the treatment with samarium iodide (SmI₂) in a mixture of tetrahydrofuran (THF) and methanol.

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For many of the above examples, formation of ketomethylene-containing peptide chains require the use of not-easily prepared starting materials and lengthy synthetic routes. Moreover, substituent incorporation, along with the required stereocontrol, is difficult in most of these synthetic approaches. For example, the requirement of using amino acid-derived aldehydes as starting material is frequently troublesome, due to their ease of epimerization. Furthermore, the availability of chiral, enantiomerically pure α-bromo carboxylic acids is limited. Therefore, most methods cannot provide a highly efficient diastereoselective route for α-side chain incorporation that would be useful for peptide isostere preparation. The development of an efficient and simple method for facilitating the conversion of easily available β-keto esters and amides into α-substituted-γ-keto esters and amides will be extremely useful for peptide isostere preparation. The development of a method that facilitates the incorporation of a
variety of substituents at the α-position could be beneficial for a host of biological relevant synthetic targets.

b) Introduction to Chain Extension Chemistry

Ketomethylene isosteres incorporated within a peptide backbone can be viewed as a γ-keto amide that requires the presence of an α-substituent. A number of strategies has been reported in the literature for the preparation of γ-keto ester and amide groups. One common strategy for the generation of the 1,4-dicarbonyl system involves utilizing donor-acceptor cyclopropanes as key intermediates. This strategy has been used to form γ-keto esters, amides and phosphonates.17 Many variations have been used to generate the donor-acceptor cyclopropane. The variations are reviewed below.

In 1974, Bieraugel’s research group reported the first chain extension reaction that used β-keto esters as starting material, in which the conversion was based on the fragmentation of a cyclopropane intermediate (Scheme 6).18 An enamine derivative 24 was generated by treatment of an amine with a β-keto ester. After applying the zinc carbenoid to the enamine derivative, an aqueous workup offered the targeted γ-keto ester 27. However, low yields for the conversion of a series of β-keto esters was reported, which constituted a serious drawback for this methodology.
Saigo's research group modified Bieraugel's method by using TMS enol ether 28 as the starting material. After exposing compound 29 to Simmons-Smith cyclopropanation conditions, a mixture of carboxylic acid derivatives 30 and 31 was isolated from saponification with potassium hydroxide, which indicated that multiple addition of the carbenoid was taking place. Treatment of compound 28 with ethyl diazoacetate and copper sulfate (cat) led to the β-carboxy-substituted-γ-keto esters 33 (Scheme 7). No simple γ-keto esters were isolated under these reaction conditions.\(^{19}\)
In 1983, Reissig's research group developed a [2+1]-cycloaddition strategy (Scheme 8), in which a methylcarbonyl-carbenoid was reacted with a silyl enol ether 34 to generate the intermediate cyclopropane. Fluoride treatment or an aqueous acidic workup provided the desired γ-keto esters 27. This method differed from those of Bieraugel and Saigo in that the starting material was derived from a methyl ketone, as opposed to the β-keto ester starting materials of the Bieraugel and Saigo studies.

**Scheme 7: Saigo’s Chain Extension Method**

**Scheme 8: Reissig’s Chain Extension Method**

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In 1987, Dowd’s research group developed a different method for the chain extension reaction of disubstituted β-keto esters 36 (Scheme 9), although the α-substituted-γ-keto ester products were generated through a similar donor-acceptor cyclopropane. The key difference involved the intermediacy of a radical in the ring expansion or chain extension reaction. This chain extension method cannot be applied to unsubstituted β-keto esters, which makes the method complementary to that of Zercher and coworkers. Furthermore, no stereoselectivity was demonstrated at the α-position, which would hinder the application of this method to peptide isostere formation.

![Scheme 9: Dowd’s Chain Extension Method](image)

In 1997, Zercher’s research group reported a simple, one-pot chain extension reaction for the formation of γ-keto esters from α-unsubstituted-β-keto esters using a zinc carbenoid for generation of the cyclopropane (Scheme 10). This zinc-mediated chain extension reaction has been successfully applied to a variety of β-keto esters and amides. Some difficulty was encountered in performing this reaction on...
α-substituted-β-keto dicarbonyl substrates, which made generation of α-substituted-γ-keto esters inefficient. However, tandem reaction sequences have been developed to target the desired α-substituted-γ-keto esters.

The mechanism of this chain extension reaction is believed to involve a donor-acceptor cyclopropane (Scheme 10). Treatment of a β-keto carbonyl compound 41 with diethyl zinc or a zinc carbenoid produces the enolate, which traps one equivalent of the carbenoid derived from methylene iodide and diethyl zinc. The cyclopropane intermediate 44 is accessed through intramolecular cycloaddition. The three-membered ring’s strain is released by fragmentation, which results in insertion of a methylene unit in the alkyl chain. The intermediacy of 45 is supported by an NMR study.22 Quenching the intermediate with a proton source, typically ammonium chloride, completes the one-pot chain extension process.

Tandem chemistry, used for α-side chain insertion, has been explored in efforts to broaden the zinc-mediated chain extension method. Reactions between the zinc-organometallic (enolate-equivalent) 45 and various aldehydes provided the predominant syn-aldol product 47, with stereoselectivity much greater than the typical Reformatsky reaction.23 Another modification involves the use of a catalytic amount of trimethylsilyl chloride, which promotes formation of a zinc homoenolate in the presence of excess carbenoid. Upon addition of a proton source, a methyl group is
incorporated at the α-position.\textsuperscript{24} Trapping with other electrophiles, like iodine,\textsuperscript{25} ketones,\textsuperscript{26} iminium ions,\textsuperscript{27} activated imines,\textsuperscript{28} is also possible and under further development.

\begin{align*}
\text{Scheme 10: Zercher's Chain Extension Method}
\end{align*}

Recently, this zinc-mediated chain extension reaction has been applied to peptide isostere preparation. Two different approaches have been studied. One involves chain extension of a β-keto ester derived from an N-protected amino acid (building off the C-terminus).\textsuperscript{29} A variety of β-keto esters 50, derived from protected natural amino acid...
acids, was prepared using a modified Claisen condensation reaction developed by Masamune and Brooks.\textsuperscript{30} Following treatment with the zinc-mediated carbenoid, dipeptide mimics 51 were generated in good to excellent yields (Scheme 11). This method was also proved to be useful for the preparation of tripeptide mimics. Four common nitrogen-protecting groups (Cbz, Fmoc, Boc, Bz) used for amino acids were shown to be tolerated in the chain extension reaction. The potential epimerization of the \(\alpha\)-amino acid’s stereocenter during the zinc-mediated chain extension was excluded based on chiral HPLC studies.

![Scheme 11: Peptide Isostere Preparation Using Zinc-Mediated Chain Extension Reaction](image)

The other approach to peptide isostere formation involved chain extension of \(\beta\)-keto amides derived from carboxyl-protected amino acid (chain extension of the \(N\)-terminus).\textsuperscript{31} A reaction between the amino acid and diketene under mild conditions offered the corresponding \(\beta\)-keto amides 53 starting material from protected or

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unprotected amino acids. Exposure of β-keto amides to the zinc-carbenoid, in a similar fashion to that involving the amino acid-derived β-keto esters, resulted in the formation of dipeptide mimics 54 in satisfactory yields (Scheme 12).

Scheme 12: Synthetic Route to the Peptide Isosteric Replacement via Chain Extension of the N-Terminus

Since the first aspect of the study, which was to test the efficiency of the chain extension reaction for the β-keto esters and amides derived from simple protected amino acids, had been successfully accomplished, the advanced task of identifying practical methods to incorporate substituents at the α-position was targeted. Both enantioselective and diastereoselective control at the α-position would be necessary for the chain extension reaction to be useful for isosteric replacement of the peptide bond. Based on the regiospecific and highly diastereoselective zinc-mediated tandem
chain extension-aldol reaction, we decided to perform a full study of this potentially useful tandem reaction on amino acid-derived substrates.

2. Results and Discussion

a) Initial Study towards Diastereoselective Zinc-Mediated Chain Extension-Aldol Reaction of \( \beta \)-Keto Amides Derived from Amino Acids

Three representative primary and secondary amino acids were selected as the starting materials for the methodological study, proline (Pro), phenylalanine (Phe) and valine (Val). Since tandem chain extension-aldol reactions are sensitive to the presence of a proton source, which would quench the enolate prior to the aldol reaction, appropriate protection of the amino acid is required. Since proline is a secondary amino acid, no further protection is required for \( 55 \), which is derived from diketene and proline methyl ester.\(^{31} \) The zinc-mediated chain extension reaction was performed on the substrate \( 55 \) using five equivalents carbenoid to test the efficiency of the chain extension reaction (Scheme 13). The targeted product \( 56 \) was prepared in high yield and was characterized by \(^1\)H and \(^{13}\)C NMR spectroscopy.

![Scheme 13: Zinc-Mediated Chain Extension Reaction of 55](image.png)

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Based on this successful result, the zinc-mediated chain extension-aldol reaction was performed by adding benzaldehyde to the chain extension intermediate 57. Surprisingly, the methyl ether 59 derived from the chain extension-aldol product was detected instead of the anticipated aldol product 58 (Scheme 14). Furthermore, benzyl alcohol was identified as a byproduct of the reaction. Reduction of benzaldehyde in the presence of carbenoids is frequently observed, although reduction of other aldehydes is not observed.

Scheme 14: Attempted Zinc-Mediated Chain Extension-Aldol Reaction Using Benzaldehyde

The formation of the methyl ether was believed to result from excess carbenoid, which reacted with the targeted aldol product 58. This assumption was confirmed by treatment of the aldol product 58, the formation of which is described below, with two equivalents of carbenoid to generate the identical methoxy-containing product 59 (Scheme 15).
Scheme 15: Preparation of Compound 59

The solution to the over-alkylation problem was to decrease the carbenoid equivalents from five to 2.5, which facilitated the chain extension reaction, yet left little or no carbenoid in the reaction solution at the time of benzaldehyde addition (Scheme 16). The isolated aldol product 62 was shown to exist as one major hemi-acetal isomer based on $^{13}$C NMR analysis. Greater than 95% diastereoselectivity in this zinc-mediated chain extension-aldol reaction was achieved, with formation of a syn-aldol product and the (S)-stereocenter at the $\alpha$-position assigned on the basis of X-ray crystallographic analysis of compound 62. The formation of the (S)-stereocenter at the $\alpha$-position meets the stereochemical requirement for the mimicry of the natural amino acid side chain.
Scheme 16: Preparation of Compound 62

Based on this encouraging result, two modifications of the aldol product 62 were performed. These modifications were designed to expand the substrate’s utility in peptide isostere preparation.

One modification involved the treatment of the aldol product 62 with trifluoroboronic etherate and triethylsilane at -78 °C for the formation of a substituted tetrahydrofuran derivative 63 (Scheme 17), which could be viewed a potential peptide isostere target. A mixture of epimers 63A and 63B was generated in a ratio of 4.4:1 during this reductive chemistry.

Scheme 17: Triethylsilane Reduction on the Compound 62
The other modification required the identification of a practical deoxygenation method for the conversion of the aldol product 62 to a mimic of the natural phenylalanine (Bn) side chain. Two radical-based methods were investigated for this goal. The use of a hydride-mediated approach was impossible due to the other ester and amide functionality. Myers’ group has described the conversion of a primary or secondary alcohol 64 to a monoalkyl diazene through Mitsunobu replacement with o-nitrobenzenesulfonyl-hydrazine (NBSH) and in situ elimination of o-nitrobenzenesulfonic acid. Loss of nitrogen and trapping of the radical with the diazene’s hydrogen atom completes the reaction (Scheme 18). However, several attempts to apply this method to compound 62 led to an unidentified mixture of products, possibly due to the reaction between the ketone and hydrazine functional groups.

\[
\begin{array}{cccc}
RCH_2OH & \xrightarrow{\text{PPh}_3, \text{DEAD, NBSH}} & RCH_2N(NH_2)SO_2Ar & > 0 \degree C \\
64 & \text{THF, -30 \degree C} & 65 \\

\left[ RCH_2\text{N=NH} \right] & -N_2 & RCH_3 \\
66 & \rightarrow & 67
\end{array}
\]

Scheme 18: Myers’ Deoxygenation Method

A two-step deoxygenation method developed by Barton’s research group involves xanthate preparation using carbon disulfide and radical reduction of the...
xanthate functionality (Scheme 19). Treatment of compound 62 with sodium hydride, followed by the addition of carbon disulfide and methyl iodide provided xanthate derivative 68 in a good yield. The AIBN-initiated radical reduction of compound 68 using tributyltinhydride afforded the final deoxygenated product 69, which mimicked both the natural phenylalanine side chain and the natural amino acid stereochemistry.

\[
\begin{align*}
\text{HO} & \quad \text{a) NaH} \\
\text{b) CS}_2 & \quad \text{c) CH}_3\text{I} \\
\text{62} & \quad \text{68}
\end{align*}
\]

Scheme 19: Barton’s Deoxygenation Method on Compound 62

Another zinc-mediated chain extension-aldol reaction on the β-keto amide (55) was explored in which formaldehyde was used as an electrophile. Due to the gaseous nature of formaldehyde, paraformaldehyde, a polymer of formaldehyde, was used in the reaction. Surprisingly, no desired aldol product 70 was generated; instead, a dimer (71) of the zinc-mediated chain extension intermediate 57 was formed (Scheme 20). The stereochemical assignment was made by X-ray crystallography.

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Scheme 20: Zinc-Mediated Chain Extension-Aldol Reaction Using Formaldehyde

The procedure was modified to transfer formaldehyde gas by cannula, formed by heating paraformaldehyde, into the solution that contained the chain extension intermediate (Scheme 21). An aldol product (de >95%) 70, exclusively existing in a ring-opened form, was obtained. The hydroxymethyl side chain mimicked the side chain of the amino acid serine, although the stereochemistry was unidentified initially.

Scheme 21: Modified Tandem Zinc-Mediated Chain Extension-Aldol Reaction Using Formaldehyde
Successful application of Barton's deoxygenation method to compound 70 provided the α-methylated derivative 73, which can be viewed as a mimic of the alanine side chain (Scheme 22).

![Scheme 22: Barton's Deoxygenation Method on Compound 70](image)

A zinc-mediated chain extension-methylation reaction, in which the zinc-organometallic intermediate is treated with catalytic trimethylsilylchloride and excess carbenoid, has been developed in our group. This method was used by Fan Su in her B.S thesis research to provide compound 73. Reacting the ketone with 2,4-DNP produced yellow crystals which were determined by X-ray crystallography to possess the (S)-configuration at the stereocenter generated in the tandem chain extension-methylation reaction (Scheme 23). The $^1$H and $^{13}$C NMR spectra of the deoxygenation product 73 and the chain extension-methylation product 74 were identical, thereby indicating that proline is an efficient chiral auxiliary for the diastereoselective zinc-mediated chain extension-aldol reaction.

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Treatment of the aldol product 76 with trifluoroboron etherate and triethylsilane at -78 °C provided the substituted tetrahydrofuran derivative 77. Once again, a mixture of isomers 77A and 77B in a ratio of 3.3:1 was generated (Scheme 24).

The zinc-mediated chain extension-aldol reaction between compound 56 and acetone was also explored (Scheme 25). Only one predominant aldol product (de >95%), existing in a ring-opened form with unknown stereocenter at the α-position,
was produced. Similar reactions to those described above were attempted on compound 78. Application of Barton’s deoxygenation method was unsuccessful with this aldol product 78 due to the inability to functionalize the sterically hindered tertiary alcohol. Efforts to mimic the valine side chain, which would have resulted from the successful deoxygenation, are underway in the research group using alternate means.

![Scheme 25: Attempted Barton Deoxygenation on Compound 78](image)

Triethylsilane reduction in the presence of trifluoroboron etherate offered the substituted tetrahydrofuran derivative 80. A mixture of isomers 80A and 80B was generated in a ratio of 3.5:1, although the stereochemistry of the two stereocenters is unknown (Scheme 26).
Lithium aluminum hydride (LAH) reduction of aldol product 80, followed by esterification with 3,5-dinitrobenzoyl chloride, was performed in an effort to gather information regarding the stereochemistry through crystal formation and X-ray structural determination (Scheme 27). However, no crystals were generated, and the stereochemistry remains unknown.

The zinc-mediated chain extension-aldol reaction between compound 56 and benzophenone was also explored (Scheme 28). Only one predominant aldol product
(de >95%) was formed. The compound existed in a ring-opened form with (S)-stereochemistry at the α-position, as assigned on the basis of X-ray structural analysis. Application of Barton's deoxygenation method was unsuccessful with this aldol product 83 due to the inability to functionalize the sterically hindered tertiary alcohol.

![Scheme 28: Attempted Barton Deoxygenation on Compound 83](image)

Triethylsilane reduction in the presence of trifluoroboron etherate offered the unexpected alcohol 85, instead of the substituted tetrahydrofuran derivative (Scheme 29). The stereochemistry generated from the reductive process was identified through X-ray crystallography.
As demonstrated by Tryder, β-keto amides derived from unprotected primary amino acid methyl esters and diketene can undergo the zinc-mediated chain extension reaction with good to excellent yield. A chiral HPLC study was used to demonstrate that no epimerization of the α-stereocenter of the amino acids occurred during the chain extension reaction. However, trapping the zinc-mediated chain extension intermediate 87 with electrophiles required additional protection of the primary amine due to the existence of an amide proton, which could quench the intermediate 87 as observed in the previous study (Scheme 30).  

Scheme 30: Active Proton Transfer during the Zinc-Mediated Chain Extension Reaction
The carbobenzyloxy (Cbz) group is a very common protecting group for amino acids in peptide synthesis and its preparation can be easily performed in aqueous sodium bicarbonate solution with benzylchloroformate in almost quantitative yield. After the reaction with diketene, β-keto amides 91 with Cbz protection were prepared (Scheme 31).

However, the zinc-mediated chain extension of this compound generated γ-keto amides in low isolated yield, apparently due to hydrolytic instability of the imide functionality (Scheme 32). This result discouraged the use of compound 91 in the zinc-mediated chain extension-aldol reaction.
Scheme 32: Attempted Preparation of γ-Keto Amides Protected by Carbobenzyloxy Group through Zinc-Mediated Chain Extension Reaction

Instead of using a carbamate type protecting group, which would incorporate imide functionality into the substrate, a benzyl (Bn) group was considered as a suitable replacement for Cbz. The reaction between primary amino acid (Phe, Val) methyl esters with benzyl bromide and potassium carbonate introduced the benzyl group on the nitrogen. A reaction with diketene provided the targeted β-keto amides 93 and 94 (Scheme 33).  

Scheme 33: Preparation of β-Keto Amides Protected by Benzyl (Bn) Group

Before conducting the study of the zinc-mediated chain extension-aldol reaction on compounds 93 and 94, two investigations were necessary. The efficiency of simple zinc-mediated chain extension reaction needed to be determined. Furthermore,
deprotection of the benzyl group from the chain extended material needed to be investigated. The chain extension reaction, performed on compound 93 and 94 with five equivalents of diethyl zinc and methylene iodide, proved to be even more efficient in the formation of γ-keto amide 95 and 96 than the reaction of the unprotected secondary amides (Scheme 34). The absence of proton appeared to aid the chain extension reaction.

\[
\text{Et}_2\text{Zn} + \text{CH}_2\text{I}_2 (5 \text{ equiv}) \rightarrow \text{scheme 34: Preparation of γ-Keto Amides Protected by Benzyl Group through Zinc-Mediated Chain Extension Reaction}
\]

Nevertheless, deprotection of the benzyl group from compound 95 was difficult even when medium pressure hydrogenolysis conditions were applied (Scheme 35). The literature confirms that it is quite challenging to cleave an amide’s benzyl group using hydrogenolysis.\(^{39}\) Other reported methods for the cleavage of Bn group would not be compatible with the ketone functional group.
Due to the unsuccessful cleavage attempts of the benzyl protecting group, a
\( p \)-methoxybenzyl (PMB) group was chosen as an alternative protecting group. Instead
of using benzyl bromide, \( p \)-methoxybenzyl chloride was reacted with the amine
nitrogen. After preparation of compounds 98 and 99, the chain extension reaction
proceeded in excellent yield (Scheme 36).

Several methods have been reported for the cleavage of PMB groups from an
amide, including refluxing with trifluoroacetic acid, \(^4\) treatment with ceric
ammonium nitrate (CAN), and treatment with tert-butyl lithium. After the consideration of functional group compatibility under such reaction conditions, ceric ammonium nitrate (CAN) was selected for the first attempt to remove the amide’s PMB group. However, the use of water and acetonitrile (1:4 ratio) as the co-solvents while stirring the reaction overnight did not result in PMB removal from the γ-keto amides 100 and 101. An unidentified mixture of products was generated during the long reaction time (Scheme 37).

\[
\begin{align*}
\text{O} & \quad \text{R} \\
\text{N} & \quad \text{R} \\
\text{PMB} & \quad \text{PMB}
\end{align*}
\]

**Scheme 37:** Attempted Cleavage of Amide’s PMB Group Using Ceric Ammonium Nitrate

After shortening the reaction time from 12 h to 30 min and monitoring consumption of starting material by thin layer chromatography (TLC), a good yield (> 60%) of the targeted products 97 and 102 was achieved (Scheme 38). The product had identical $^1$H and $^{13}$C NMR spectra to the compound prepared through zinc-mediated chain extension reaction of unprotected β-keto secondary amide.
The zinc-mediated chain extension-aldol reaction was performed on the β-keto amide 98 using formaldehyde as the electrophile. Two inseparable aldol products 103A and 103B (in a ratio of 1:1), existing in ring opened forms, were produced. No diastereoselectivity was obtained in the aldol reaction (Scheme 39).

Direct removal of the PMB group of aldol products 103A and 103B with ceric ammonium nitrate (CAN) was not successful. An unidentifiable mixture was formed, which might be attributable to the strong oxidizing ability of CAN (Scheme 40).43

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Based on this unexpected result, a tert-butyldimethylsilyl (TBDMS) group, which is a common protecting group for an alcohol, was used to protect the aldol products prior to the attempted cleavage of the PMB group. However, the CAN oxidation was still unsuccessful in removing the PMB group and producing the secondary amide (Scheme 41).
Eventually, the protecting group was switched from TBDMS to the TBDPS (tert-butyldiphenylsilyl) group for the purpose of increasing the silyl ether 107's stability.\textsuperscript{45} This change allowed for the cleavage of the PMB group. The two diastereomers 107\textsubscript{A} and 107\textsubscript{B} were able to be separated by column chromatography (Scheme 42); however, stereochemical assignment of the two isomers was not possible.

\textbf{Scheme 42: Modified Cleavage of Amide’s PMB Group Using Ceric Ammonium Nitrate}

Though deprotection of the TBDPS group was not explored in an effort to release the hydroxymethyl group (serine mimic), tetrabutylammonium fluoride (TBAF) treatment is typically used to facilitate the cleavage (Scheme 43).\textsuperscript{44}
Barton's deoxygenation method was successfully applied to the aldol products 103A and 103B in order to generate the side chain mimic for alanine. The intermediate xanthates 110A and 110B were separated using column chromatography (Scheme 44), and the deoxygenation reactions performed on the two isomers 111A and 111B separately.

Scheme 43: Proposed Cleavage of TBDPS Group Using Tetrabutylammonium Fluoride Treatment

Scheme 44: Barton's Deoxygenation Method on Compounds 103A and 103B
When the zinc-mediated chain extension-aldol reaction with benzaldehyde was performed on substrate 98, minimizing the equivalents of carbenoid from 5 to 2.5 was required to prevent formation of the aldol-methylation by-product. Inseparable aldol products 112A and 112B (ratio 1:1), existing in hemiacetal forms, were formed with unknown stereochemistry (Scheme 45). It was unclear whether the stereoisomers were formed due to poor syn/anti aldol selectivity, or due to poor enolate facial selectivity. Furthermore, the stereochemical analysis was complicated by the appearance of amide bond rotamers.

![Scheme 45: Modified Tandem Zinc-Mediated Chain Extension-Aldol Reaction](image)

Barton’s deoxygenation method was also successfully applied to the aldol product 112A and 112B, which provided a side chain mimic of phenylalanine. The intermediate xanthates 113A and 113B were separated using column chromatography. Reaction of the purified xanthates provided the α-benzyl amide 114A and 114B (Scheme 46). The two reduction products were isomeric, indicating that the poor stereoselectivity in the aldol reaction was due to poor enolate facial selectivity.
Scheme 46: Barton's Deoxygenation Method on Compounds 112A and 112B

In summary, the study on the zinc-mediated chain extension-aldol reaction of \( \beta \)-keto amides derived from amino acids indicated that proline was a good chiral auxiliary for the chain extension-aldol reaction. High diastereoselectivity, both in terms of enolate facial selectivity and \textit{syn/anti} aldol selectivity, was achieved using a proline-modified substrate. In contrast, neither valine nor phenylalanine provided good stereocontrol in the chain extension aldol reaction. The challenge in removing proline, which requires harsh acidic conditions, prevents further derivatization and the preparation of tripeptide or tetrapeptide mimics. The utilization of another efficient method...
and easily removal chiral auxiliary, which provides excellent diastereocontrol and is easily removed, for the chain extension aldol reaction was necessary.

b) Study towards Diastereoselective Zinc-Mediated Chain Extension-Aldol Reaction on β-Keto Imides Derived from Amino Acids

Theberge had used the chain extension reaction approach for the synthesis of tripeptide 117 and tetrapeptide mimics (Scheme 47). His approach involved the conversion of the amino acid’s carboxy terminus into a β-keto ester, which was chain extended to generate the γ-keto ester. With this approach, both the N and C-terminus are available for further manipulation. However, Theberge did not attempt to incorporate side chain mimics in the isostere. The development of a diastereoselective zinc-mediated chain extension-aldol reaction on a substrate with a removable chiral auxiliary on the carboxylic terminus might allow the incorporation of side chain mimics with stereocontrol. Furthermore, the ability to derivatize both the N and C termini of the peptide mimic would greatly aid the utility of the method.
Scheme 47: Theberge’s Synthesis of Tripeptide Mimic using Zinc-Mediated Chain Extension Reaction

Proline protected by the tert-butoxycarbonyl (Boc) group (118) was selected as the starting material for this study, since only one protecting group was needed. No studies had been performed on the ability of proline, or any other chiral amino acid, to influence the stereochemistry at the α-position during tandem reaction sequence. The initial studies were designed to investigate the stereochemical influence of the proline. Masamune-Brooks reaction with monobenzyl malonate (MBM) offered the targeted β-keto benzyl ester 119 (Scheme 48). The benzyl ester was selected to facilitate the subsequent deprotection and amino acid coupling reactions. The removal of the benzyl ester can be performed using mild hydrogenolysis. In contrast, the cleavage of a methyl ester, usually performed under strongly basic conditions, could cause the epimerization of the amino acid’s α-proton.
Scheme 48: Preparation of β-Keto Benzyl Ester 118 Using Masamune-Brooks Reaction

A tandem zinc-mediated chain extension-aldol reaction was performed on substrate 119 with formaldehyde in an effort to generate serine mimics (Scheme 49). Two inseparable diastereomers were formed, which indicated that the remote stereocenter of proline did not affect the diastereoselectivity of the aldol reaction.

Scheme 49: Zinc-Mediated Chain Extension–Aldol Reaction on Compound 119

In an effort to facilitate product separation and subsequent amino acid coupling reactions, the TBDMS group was used to protect the primary alcohol generated in the chain extension-aldol reaction. After the formation of compounds 121A and 121B, hydrogenolysis of benzyl ester offered the carboxylic acid derivative 122A and 122B. The acid was coupled with (S)-phenylalanine methyl ester using

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1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) to provide the tripeptide ketomethylene containing mimics 123A and 123B, which were separated using column chromatography (Scheme 50).

Scheme 50: Synthesis of Tripeptide Mimic using Zinc-Mediated Chain Extension-Aldol Reaction

As discussed previously (Scheme 30), the presence of an active proton source in the amino acid would quench the chain extension intermediate; therefore a suitable protecting group for the primary amine was required. The phthalimide protecting group was selected, since it would avoid the rotamer phenomenon (two identical functional groups on nitrogen atom) which complicates NMR spectral interpretation. A three-step synthetic approach is illustrated below for the preparation of the phthalyl-protected valine (Scheme 51): ring opening of phthalic anhydride using the
trifluoroboron ether complex provided the achiral half-ester 125. Methyl 2-((succinimidooxy)carbonyl)benzoate 126 was prepared by reaction of compound 125 with N-hydroxysuccinimide using dicyclohexylcarbodiimide (DCC) as the coupling reagent. The compound was allowed to react with the sodium salt of (S)-valine to offer the product 127.49

![Scheme 51: N-Phthaloylation of (S)-Valine](image)

A Masamune-Brooks reaction with monobenzyl malonate (MBM) generated the targeted β-keto benzyl ester 128. When the zinc-mediated chain extension reaction was performed, the product was the tricyclic compound 130, which was identified by X-ray crystallography (Scheme 52). The spontaneous attack onto the imide’s carbonyl group by the enolate-equivalent appears responsible for the formation of compound 130.
An identical result was observed when (S)-phenylalanine was used as the starting material instead of valine. Though the unexpected formation of the bicyclic derivative excluded the possibility of using the phthalimide protecting group for the zinc-mediated chain extension-aldol reaction, the formation of this interesting bicyclic compound was efficient.

The tert-butoxycarbonyl (Boc) and p-methoxybenzyl (PMB) groups were selected for protection of the amino acids in the ensuing chain extension-aldol reaction study, since selective removal of these two protective groups appeared possible. Sodium borohydride reduction of the iminium ion derived from (S)-alanine and anisaldehyde provided compound 132. The incorporation of the Boc group
using di-tert-butyl dicarbonate offered compound 133. However, after preparation of
the β-keto benzyl ester 134 using the Masamune-Brooks protocol, the zinc-mediated
chain extension reaction was not successful. Starting material was recovered (Scheme
53).

Switching the protecting group from p-methoxybenzyl (PMB) to benzyl (Bn) did
not improve the efficiency of chain extension reaction. Therefore, the
benzyloxy carbonyl (Cbz) group was considered as a replacement for the Boc group.
Compound 137 was prepared followed similar chemistry described above (Scheme
54), although the allyl ester was incorporated as part of the β-keto ester.
Scheme 54: Preparation of Compound 137

The zinc-mediated chain extension reaction was successfully performed on substrate 137 and trapping the chain extension intermediate with formaldehyde provided two diastereomers 138A and 138B, which is consistent with the poor stereoselectivity observed in the previous study on the proline derivative (Scheme 55).

Scheme 55: The Zinc-Mediated Chain Extension-Aldol Reaction on Substrate 137

*tert*-Butyldiphenylsilyl (TBDPS) protection of compounds 138A and 138B was performed in order to simplify NMR spectral interpretation and to facilitate amino acid coupling reactions. The allyl ester was cleaved using palladium
tetrakis(triphenylphosphine) and pyrrolidine to produce carboxylic acids 140A and 140B.\textsuperscript{51} The coupling reaction with alanine methyl ester hydrochloride using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) provided the tripeptide ketomethylene mimic (141A and 141B) of the alanine-serine-alanine sequence, albeit as a mixture of diastereomers (Scheme 56).

\includegraphics{Scheme_56.png}

**Scheme 56: Synthesis of Tripeptide Mimics Using Zinc-Mediated Chain Extension-Aldol Reaction**

Incorporation of an asparagine residue on the \textit{N}-terminus would provide a tetrapeptide mimic of the Human cytomegalovirus (HCMV) protease cleavage site.
More detailed rationale for targeting this tetrapeptide and for the inclusion of the \(N,N\)-dimethylasparagine residue will be presented later. The \((S)\)-asparagine derivative was prepared in a two-step reaction sequence to generate the carboxylic acid 144 needed for the preparation of the tetrapeptide mimic (Scheme 57). The coupling reaction between the commercially available Boc-protected aspartic acid benzyl ester 142 and \(N,N\)-dimethylamine hydrochloride provided compound 143. Palladium-catalyzed hydrogenolysis offered the targeted asparagine derivative 144.

![Scheme 57: Synthesis of \(N,N\)-Dimethyl Asparagine Derivative 144](image)

The selective removal of the Cbz group was successfully performed using hydrogen and catalytic 10% palladium on carbon to produce compounds 145A and 145B. However, the amino acid coupling reaction between compound 145 and 144 proceeded in a low yield, possibly due to the steric hindrance of the tertiary amine 145 (Scheme 58).\(^{22}\) Removal of the PMB group at an earlier stage appeared essential for the synthesis of the peptide mimic. Since removal of the PMB group would also aid

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NMR interpretation due to the exclusion of rotamer forms, the early removal of the PMB group was planned in the future synthetic approach.

![Chemical structures](image)

**Scheme 58: Attempted Synthesis of Tetrapeptide Mimic**

A synthetic strategy was designed to address the numerous observations made in the study. The PMB group would be removed earlier in the reaction sequence, in order to facilitate the peptide coupling to the N-terminus. Furthermore, a diastereoselective aldol reaction was necessary to generate a single product isomer, which would simplify all aspects of analysis. Though proline was shown to be an excellent chiral auxiliary in previous studies, the harsh condition required to remove the proline residue and the potential for epimerization of the α-position of amino acids under the harsh condition required development of another chiral auxiliary for the zinc-mediated chain extension-aldol reaction.
Evans' auxiliaries, derived from chiral amino acids, have been used widely for asymmetric synthesis. The incorporation of chiral oxazolidinone onto the amino acid chain through a Masamune-Brooks reaction would be attractive for formation of the chiral β-keto imide needed for diastereoselective chain extension-aldol reactions. The first approach to the carboxylic acid (149) required for a Masamune-Brooks reaction involved a reaction between (S)-4-benzyloxazolidin-2-one 147 and trimethylsilylchloride, followed by exposure to Meldrum's acid (Scheme 59). However, an unexpected compound was generated instead of the targeted compound 149. The unexpected compound was eventually identified as compound 150 based on X-ray crystallography.

\[
\begin{align*}
\text{147} & \xrightarrow{\text{Me}_3\text{SiCl}} \text{148} & \xrightarrow{\text{Cu, CuCl}_2} & \text{149} \\
\text{150} & 
\end{align*}
\]

Scheme 59: Attempted Synthesis of Compound 149

The preparation of compound 149 was eventually accomplished using an indirect approach. Monobenzyl malonate 151 was converted into the acyl chloride, which was
heated with oxazolidinone 147 to produce compound 152. The hydrogenolysis reaction offered the monooxazolidinone malonate 149. However, many attempts at the attempted preparation of a β-keto imide via a Masamune-Brooks reaction with the monooxazolidinone malonate 149 were not successful (Scheme 60).

![Scheme 60: Attempted Synthesis of Compound 154](image)

After much effort, a modified Claisen condensation reaction was successful in generating the targeted β-keto imide 154 (Scheme 61). A chiral HPLC study of the β-keto imide 154, derived from enantiomerically pure (S)-alanine, indicated that no epimerization of the alanine α-stereocenter took place during the Claisen condensation process. Analogous compounds derived from racemic alanine were used for reference.
Scheme 61: Synthesis of β-Keto Imide 154 Using Modified Claisen Condensation

The zinc-mediated chain extension-aldol reaction was performed on the β-keto imide 154 using solid paraformaldehyde as the electrophile. Surprisingly, none of the desired aldol product was isolated from the reaction mixture. One predominant cyclopropanol derivative 159 was separated from the crude mixture. The reason for this unusual reactivity could be attributed to enhanced enolate character associated with the imide functional group. The mechanism for the formation of compound 159 was proposed to involve spontaneous alkylation of chain extension intermediate 155 with the excess carbenoid, followed by nucleophilic attack of the homoenolate onto the carbonyl group, which generated the cyclopropanol structure (Scheme 62). The possibility of preventing cyclopropanol formation by controlling reaction time was excluded due to the coexistence of cyclopropanol derivative 159 and the starting β-keto imide 154.
Scheme 62: Proposed Mechanism for the Formation of Cyclopropanol Derivative 159

Formation of the cyclopropanol compound was unusual for a number of reasons. When β-keto esters and amides are used as starting materials for the chain extension, the zinc-organometallic intermediate (enolate equivalent) is very stable and does not undergo additional reactions with excess carbenoid. The rapid reaction of the zinc intermediate of the imide with carbenoid is possibly due to its ability to chelate zinc between the carbonyls. Furthermore, intramolecular cyclization of the homoenolate to provide a cyclopropanol has not been observed with ester or amide groups. The imide functionality is a better electrophile and appears to react more like a ketone than an
ester. A similar, although not identical, result was observed in the chain extension reaction performed on substrate 160 (Scheme 63). In this example, the chain extension intermediate underwent further alkylation to generate the methylation product 162, in addition to the simple chain extension product 161. However, in this reaction no cyclopropane product was isolated.

Scheme 63: Zinc-Mediated Chain Extension Reaction on β-Keto Imide 160

These unexpected results inspired the study of a chain extension reaction in which the imide carbonyl takes the place of the ketone. A possible mechanism is illustrated below (Scheme 64). With this substrate, the cyclopropanol intermediate 163 is part of a donor-acceptor system, as opposed to 155 or 156. Donor-acceptor cyclopropane 163 will fragment to complete the chain extension. A tandem chain extension-aldol reaction provided 166 as a single unidentified diastereomer. This method might be useful for the preparation of substituted γ-lactones, like the paraconic acids.\textsuperscript{56}
Fortunately, a solution to the overalkylation/cyclopropanol formation problem was identified. After formation of the carbenoid, excess paraformaldehyde (10 equiv to the starting β-keto imide 154) was added prior to the addition of β-keto imide 154. The reaction of the enolate with the aldehyde was preferred to homoenolate formation. The successful zinc-mediated chain extension-aldol reaction provided a single aldol product 167, which existed mostly in the ring-opened form, although the stereochemistry at the α-position was unknown (Scheme 65). The $^1$H and $^{13}$C NMR spectra were difficult to interpret due to the presence of two rotamers and the equilibrium between ring-opened and hemiacetal forms. Electrospray ionization (ESI)
MS, however, supported the structural assignment of compound 167 due to the presence of an ion peak with $m/z = 611$ (M+Na$^+$).

Scheme 65: Modified Zinc-Mediated Chain Extension-Aldol Reaction

Cleavage of the PMB protecting group was expected to facilitate NMR spectral interpretation through biasing the rotamer populations. Amino acid coupling was also expected to be simplified without the PMB group on the amide. Therefore, cleavage of the amide's PMB group using ceric ammonium nitrate (CAN) was undertaken. However, the removal of the imide's PMB group with CAN did not provide the target compound 168. A lactone product 169 was generated under these reaction conditions. The structural assignment of compound 167 was confirmed by removal of the Evans chiral auxiliary from 169 through treatment with lithium hydroxide and hydrogen peroxide$^{52b}$ to offer compound 170, tetrahydro-5-oxofuran-3-carboxylic acid, which is known in the literature (Scheme 66).$^{56}$ Evidence of the $\alpha$-stereocenter generated from the zinc-mediated chain extension-aldol reaction was obtained by measurement of the optical rotation ($[\alpha]_{D}^{25} = +40.0$ (c = 0.001 g/mL, MeOH)). The literature report for
(R)-170 has a rotation of \([\alpha]^{25}_D = +47.1\) (c = 0.14 mmol/mL, MeOH), which allowed assignment of the stereochemistry of the α-position of compound 170 as (R). This stereochemical result is consistent with the reported aldol reaction using the Evans auxiliary in the literature\(^{52a}\). Therefore, in order to mimic natural amino acid stereochemistry, which is (S), the Evans auxiliary derived from the (R)-amino acids must be used.

![Scheme 66: Cleavage of Imide's PMB Group Using CAN](image)

Similar chemistry was performed on a variety of substrates with different functional groups in order to obtain more detailed information about this unusual CAN-mediated chemistry. Reaction between aldol-product 172 and CAN provided the identical lactone 169, which means the existence of the PMB group is not necessary for lactone formation (Scheme 67).
Triethylsilane reduction of the aldol product 172 with known stereochemistry provided the substituted tetrahydrofuran derivative 173A and 174B in a 1:1 mixture of isomers (Scheme 68). The proline stereocenter does not appear to control the reduction of the hemiacetal.

Scheme 68: Formation of Substituted Tetrahydrofuran Derivative 174A and 174B
However, when the triethylsilane reduction was performed on the aldol product derived from (S)-alanine, an unidentified product was generated instead of the targeted substituted tetrahydrofuran derivative 185 (Scheme 69). Analysis by ESI MS ($m/z=595, (M+Na^+)$) and $^{13}$C NMR spectra (no ketone resonance) indicated a possible intramolecular Friedel-Crafts reaction, which means a different protecting group would be needed in place of the PMB group for the formation of the tetrahydrofuran derivative. The assigned structure of 186 is speculated. Additional evidence would be necessary to confirm compound 186.

Scheme 69: Attempted Formation of Substituted Tetrahydrofuran Derivative 185

The $\beta$-keto benzyl ester 175 and methyl ester 178 were prepared from PMB-protected-Cbz-(S)-alanine. Compounds 176 were obtained as a mixture of diastereomers (approx 1:1) after the tandem-chain extension aldol reaction. Treatment
of these aldol products (176A and 176B) with CAN provided the racemic lactone, which indicated that the Evans auxiliary is not required for CAN-mediated lactonization (Scheme 70).

Scheme 70: Preparation of Compound 177

Oxidative cyclization of compound 178, derived from the methyl ester, was successful in providing lactone 179; however, its high volatility resulted in low mass recovery (Scheme 71)

Scheme 71: Attempted Cleavage of Imide's PMB Group Using CAN

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Two simple aldol products 180 and 181 were prepared to determine whether the heteroatom (nitrogen) α to the ketone played a role in this reaction. No lactone was generated when the aldol products were subjected to the reaction conditions used for oxidative cyclization (Scheme 72). Therefore, it was confirmed that a heteroatom at the α-position to the ketone is necessary for lactone formation. Subsequent work by Walls and Jacobine has provided preliminary evidence that oxygen functionality α-to the ketone can also facilitate the oxidative cyclization.57

![Scheme 72: Attempted Lactone Formation Using CAN](image)

For the purpose of mimicking the natural stereochemistry of a peptide backbone, an Evans chiral auxiliary derived from (R)-phenylalanine was necessary to induce formation of the aldol product with an (S)-stereocenter. This chiral auxiliary was generated via standard literature methods.58 A modified Claisen-condensation reaction provided the β-keto imide and zinc-mediated chain extension reaction
produced only one predominant aldol-product. A diastereomeric ratio of greater than 95:5 was estimated from the $^{13}$C NMR spectrum of the crude reaction material. Compound 183 was generated through treatment with CAN and the chiral auxiliary was cleaved to provide compound 184 (Scheme 73). The optical rotation of 184 was $-35.0$ (c = 1.2 mg/mL, MeOH), which allowed assignment of the desired ($S$)-configuration at the aldol stereocenter.

![Scheme 73: Preparation of (S)-Paroconic Acid](image)

Similar chemistry was performed on the aldol-product 188, produced from paraformaldehyde and the (S)-proline derived β-keto imide (Scheme 74). The usage of the auxiliary generated from (R)-phenylalanine provided the identical lactone 183.
With the successful development of diastereoselective zinc-mediated chain extension-aldol reactions using an Evans chiral auxiliary, a specific compound was targeted in an effort to test the methodology and overall strategy.

c) Synthesis of a Proposed Inhibitor of Human Cytomegalovirus (HCMV) Protease Using Diastereoselveteive Zinc-Mediated Chain Extension-Aldol Reaction

Human cytomegalovirus (HCMV) is a pathogen which is a member of the β-herpes subfamily of the herpes virus family (Herpesviridae). HCMV can be spread by human-to-human contact and it has been estimated that, within the United States, greater than 50% of the adult population and about 20% of the pre-pubescent population is infected. Serious health risks (retinitis, pneumonia, and death) can be
caused by HCMV, especially in the immunocompromised and immunologically immature patients, like transplant recipients, newborn infants, and AIDS/HIV-infected patients. The generation and reproduction of HCMV relies upon a unique 28-kDa serine protease. An amino acid sequence of Val-Asp-Ala-Ser is necessary for this serine protease's site-specific recognition, resulting in cleavage of the Ala-Ser bond (Figure 2).

Figure 2: Preferred Site of HCMV Protease Cleavage

The development of a successful strategy for this protease's inhibition will constitute an attractive method for disrupting the HCMV life cycle. A study has suggested that peptide isosteres could be effective inhibitors of HCMV protease; however, no ketomethylene isosteric group was used in that study. Since the ketomethylene isostere has been successful in protease inhibition, a tetrapeptide mimic of the Asp(N,N-dimethyl)-Ala-Ser-Ala-Ala sequence was proposed as a potential inhibitor of HCMV protease (Figure 3). The use of N,N-dimethyl asparagine instead of asparagine was targeted due to the report of enhanced inhibition in the
Furthermore, replacement of the asparagine’s two amide protons with a methyl group should obviate the need to protect the asparagine’s amide side chain.

**Isosteric Amide bond Replacement**

![Chemical structure](image)

**Figure 3: The Proposed Inhibitor of Protease of HCMV**

The successful diastereoselective preparation of a dipeptide mimic of alanine-serine, as described above (Scheme 65), offered the possibility for the preparation of the proposed HCMV protease inhibitor by coupling an alanine residue to the C-terminus and $N,N$-dimethyl asparagine to the N-terminus. The protection of the aldol product 182 with the TBDPS group was needed for the successful removal of the imide’s PMB protecting group, while avoiding CAN-mediated oxidative lactone formation. Compound 192 was successfully prepared in good yield by the reaction with tert-butyldiphenylsilyl chloride followed by CAN oxidative cleavage (Scheme 75).
Scheme 75: The Imide's PMB group removal using CAN

The typical removal of the Evans auxiliary with lithium peroxide to generate the carboxylic acid 197 was not successful. A Bayer-Villiger reaction was proposed based on the isolation of products 196, 147 and 195 from the mixture (Scheme 76).
The use of lithium hydroxide instead of lithium peroxide for the removal of the Evans auxiliary was considered. Treatment with excess (6 equiv) lithium hydroxide resulted in epimerization of a stereocenter, most likely that of the (S)-alanine's α-position. By reducing the equivalents of lithium hydroxide from six to one and by careful control of the addition time and reaction temperature, the Evans auxiliary was successfully cleaved with no epimerization. The coupling reaction between carboxylic acid 197 and alanine methyl ester hydrochloride provided the tripeptide mimic 198 as a single diastereomer (Scheme 77).
The removal of the TBDPS group was tested on this compound and shown to be successful (Scheme 78). The product possesses three of the four amino acids proposed for HCMV protease recognition and will be submitted for testing against HCMV protease.

Removal of the Cbz group by hydrogenolysis was performed in methanol. Anhydrous p-toluenesulfonic acid was used to trap the newly generated amine and
avoid formation of a dimeric product derived from the free amine and ketone functional groups. However, an unidentified mixture of products was formed possibly due to the instability of the TBDPS group in the acidic methanolic environment (Scheme 79).45

![Chemical structure of 198](image)

**Scheme 79: Attempted Removal of Cbz Group Using Hydrogenolysis in Methanol**

By switching the hydrogenolysis solvent from methanol to 2-propanol, the reaction provided 199. Amino acid coupling between 199 and the asparagine derivative 144 provided the TBDPS-protected tetrapeptide mimic 200 (Scheme 80).

![Chemical structure of 198 and 199](image)

**Scheme 80: Synthesis of Tetrapeptide Mimic 200**

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Treatment of compound 200 with excess sodium methoxide provided two diastereomers (Scheme 81). The comparison of $^1$H and $^{13}$C NMR spectra between compound 200 and the mixture of diastereomers indicated that the synthetic route developed for the synthesis of the tetrapeptide mimic proceeded with greater than 95% diastereoselectivity.

![Chemical structure of compound 200 and 201]

Scheme 81: Racemic Study on Compound 200

The removal of the TBDPS group from compound 200 was successfully performed to offer the proposed inhibitor, existing in hemiacetal form, of HCMV protease (Scheme 82). The high polarity of the final compound resulted in low mass recovery when the compound was purified by column chromatography. Efforts to improve mass recovery and improve the isolated yield are still underway.
Scheme 82: Synthesis of Tetrapeptide Mimic 202

In summary, the diastereoselective zinc-mediated chain extension-aldol reaction using proline or an Evans chiral auxiliary has been demonstrated to be of practical synthetic utility in the construction of highly functionalized ketomethylene-containing dipeptide mimics. The incorporation of ketomethylene isosteric amide bond replacement into tripeptide and tetrapeptide analogues was easily accomplished when using this strategy. A facile synthetic route has been developed for a proposed inhibitor for Human Cytomegalovirus (HCMV) protease.
CHAPTER II

FORMAL SYNTHESIS OF (+)-BREFELDIN A

1. Introduction

a) Introduction to (+)-Brefeldin A

(+)-Brefeldin A (Figure 4), a bicyclic compound with a 13-membered macrocyclic structure, is a fungal metabolite. The isolation of (+)-Brefeldin A from the fungi (such as Penicillium decumbens, P. brefeldianum, and Phyllosticta medicaginis) was first reported in 1958,\textsuperscript{63} and the structure and stereochemistry of (+)-Brefeldin A were clarified by X-ray crystallography in 1971.\textsuperscript{64}

\[ \text{(+)-Brefeldin A} \]

\[ \text{Figure 4: Structure of (+)-Brefeldin A} \]

A wide range of intriguing biological properties of this interesting molecule has been reported, such as antiviral, cytostatic, antitumor, and antibiotic effects.\textsuperscript{65}
Furthermore, a recent study has demonstrated that (+)-Brefeldin A can drive Golgi complex disassembly and redistribution to the endoplasmic reticulum, and can inhibit protein transport to post-Golgi compartments in the cell\textsuperscript{66} (+)-Brefeldin A has also been investigated as an anticancer agent\textsuperscript{67}

i) Previous Representative Synthetic Approaches to (+)-Brefeldin A

(+)-Brefeldin A has two \textit{trans} double bonds, five \textit{sp}\textsuperscript{3} stereogenic centers, and a 13-membered macrocyclic lactone. As a result of this challenging structure and broad biological activity, many research groups have developed synthetic approaches to (+)-Brefeldin A\textsuperscript{68}, including the first reported total synthesis of (±)-Brefeldin A by Cory's research group in 1976\textsuperscript{68a}. Corey's synthetic approach used a known bicyclic ester 204 as the starting material (Scheme 83). After hydroboration with borane and oxidation with chromic acid, treatment with triethylamine provided the enone 205. Reaction between the Gilman cuprate and the sodiomalonate derivative of enone produced the desired conjugate addition product 206. After lithium borohydride reduction, the alcohol was protected as a methoxyethoxymethyl ether 207. Following saponification with sodium hydroxide, treatment with \textit{n}-butyllithium, oxygenation in the presence of trimethyl phosphite and oxidative decarboxylation, the methyl ester derivative 208 was prepared using diazomethane.
Diisobutylaluminum hydride (DIBAL-H) reduction of the ester and oxidation using the Collins reagent provided the aldehyde 210. Addition into the carbonyl by the lithiated alkene (prepared by treatment of an organotin compound with n-butyllithium) and hydroxyl group protection with methoxyethoxymethyl chloride generated the compound 211. Removal of methylthiomethylene protecting group was successfully accomplished using mercuric chloride and calcium carbonate to offer compound 212. After oxidation with Collins reagent and deprotection of the silyl ether with a fluoride source, compound 213 was prepared using the successful
Yamaguchi macrolactonization for the conversion from A-brefeldinoic acid to (±)-Brefeldin A. Deprotection of the MEM group with titanium chloride and selective oxidation of the allylic alcohol with manganese (IV) oxide preceded the sodium borohydride’s stereoselective reduction to form the required 4α-alcohol. (±)-Brefeldin A was prepared through removal of the MEM group (Scheme 84). The efficient conversion of compound 214 to (±)-Brefeldin A has inspired efforts of other research groups to complete the formal synthesis of Brefeldin A through targeting 214 as a key synthetic intermediate.
**Scheme 84: The First Total Synthesis of (±)-Brefeldin A (Part II)**

Subsequent to Corey’s report on the synthesis of the racemic material, many synthetic approaches have been developed for the stereoselective synthesis of enantiomerically pure (+)-Brefeldin A. For example, the synthetic approach with the fewest steps was reported by Trost’s research group in 2002 (Scheme 85 and...
The synthesis of 4-naphtyloxybutenolide 218 was accomplished through a palladium-catalyzed asymmetric allylic alkylation in the presence of chiral ligand 217. A palladium-catalyzed trimethylenemethane cycloaddition offered the cis-cyclopentane 219. Oxidative cleavage and DIBAL reduction provided the alcohol derivative 220 with good diastereoselectivity. After the protection with a TBDMS group, a Weinreb amide was generated from the lactone precursor. Treatment with DBU caused the epimerization of the aldehyde and provided the trans-cyclopentane stereochemistry required for compound 221. A lithium anion, derived from ethyl propiolate, was added to the aldehyde to produce the propargyl alcohol 222. Ruthenium-catalyzed hydrosilylation and cesium fluoride desilylation provided the compound 223 in one pot. After protection with TBDMS group, a transformation from Weinreb amide to aldehyde was successfully performed with DIBAL-H to offer aldehyde 224.
The other portion (lower side chain) of this convergent synthesis to (+)-Brefeldin A was also initiated via asymmetric allylic alkylation. The reaction between crotol

a) 2.5% Pd(OAc)$_2$, 20% P(OiPr)$_3$, toluene. b) NaIO$_4$, 5% OsO$_4$. c) DiBAL, BHT, toluene.
d) TBSOTf, pyridine. e) iPr$_2$MgCl, MeO(Me)NH$_2$Cl, THF. f) DBU. g) LiCCO$_2$Et.

THF/HMPA. h) (EtO)$_3$SiH, 1% Cp*Ru(CH$_3$CN)$_3$PF$_6$, CH$_2$Cl$_2$, CsF (96%). i) TBSOTf,
pyridine.

j) Dibal, THF

Scheme 85: Trost's Total Synthesis of (+)-Brefeldin A (Part I)
carbonate 225 and \( p \)-methoxyphenol provided allylic ether 226. Hydroboration-oxidation, oxidation to the aldehyde, and in situ treatment with the Wittig reagent offered the \( \alpha,\beta \)-unsaturated ethyl ester derivative 227. Treatment with sodium borohydride in the presence of catalytic nickel dichloride resulted in 1,4-reduction of compound 227. DIBAL-H reduction of the ester generated the primary alcohol 228. Mitsunobu coupling between compound 228 and 1-phenyl-5-thiotetrazole, followed by oxone oxidation, offered the sulfone derivative 229. Modified Julia coupling of compound 229 and 224 proceeded successfully to give predominantly the trans-olefin product 230 \((E/Z > 12/1)\). Cleavage of the PMP group by treatment with ceric ammonium nitrate (CAN) and ester hydrolysis with sodium hydroxide solution generated the precursor 231 for Yamaguchi macrolactonization. Finally, silyl deprotection with tetrabutylammonium fluoride (TBAF) produced the targeted compound: \((+)-\text{Brefeldin A}\) (Scheme 86).
a) \( \rho \)-Methoxyphenol, 0.25% \( \text{Pd}_2\text{dba}_3\)-CHCl\(_3\), 0.75% \( \text{PPh}_3\), toluene. b) 9-BBN, THF, then \( \text{H}_2\text{O}_2\), aq NaOH. c) PCC, then \( \text{EtO}_2\text{CC}\text{H}\text{PPh}_3\), d) \( \text{NaBH}_4\), MeOH, 5% NiCl\(_2\). e) DIBAL-H, THF. f) DIAD, \( \text{PPh}_3\), 1-phenyl-5-thioltetrazole. g) Oxone, MeOH. h) KHMDS, DME, then 224. i) C.A.N.. j) 1N NaOH. k) MsCl, Et\(_3\)N, 2,4,6-trichlorobenzoyl chloride, 4-DMAP. l) TBAF, THF.

Scheme 86: Trost’s Total Synthesis of (+)-Brefeldin A (Part II)

b) Introduction to Formation of \( \alpha,\beta \)-Unsaturated-1,4-Dicarbonyl Compounds

A variety of natural products containing the \( \alpha,\beta \)-unsaturated-\( \gamma \)-hydroxy-macrolide or the \( \alpha,\beta \)-unsaturated-\( \gamma \)-keto-macrolide functional group has been reported in the literature (Figure 5), like (+)-Brefeldin A 203\(^\text{63}\), (+)-Patulolide A 232,\(^\text{69}\) (-)-Patulolide B 233,\(^\text{70}\) (-)-Pyrenophorin 234\(^\text{71}\) and
(-)-A26771B 235. All of these macrolides would require suitable method for the formation of α,β-unsaturated-γ-keto system within macrocyclic systems. Although few methods have been reported for the specific generation of α,β-unsaturated-γ-keto-lactones, many approaches have been developed for the formation of α,β-unsaturated-γ-keto esters. Some of the more general methods are described below.

![Compounds](image)

**Figure 5:** Natural Products Containing α,β-Unsaturated-γ-Hydroxy or Carbonyl Functional Groups

One method for the formation of α,β-unsaturated-γ-keto esters involved the treatment of γ-keto esters 27 with bromine under photochemical conditions, which
provided the β-bromo-γ-keto esters 236. After elimination with triethylamine, the targeted esters 237 were prepared with only trans-double bond formation (Scheme 87). However, the unavailability of diverse 1,4-dicarbonyl compounds and poor regio/chemo-selectivity in the bromination reaction limits application of this method.

\[
\begin{align*}
\text{Scheme 87: Generation of α,β-Unsaturated-γ-Keto Esters Using Photochemical Bromination and Elimination}
\end{align*}
\]

A modification of this method was reported by Reissig, whose reaction was designed to overcome the shortcoming of unavailable 1,4-dicarbonyl compounds (Scheme 88). Easily-prepared trimethyl(vinylxy)silane derivatives 238 were used to generate the various siloxy-substituted methyl cyclopropanecarboxylate 239. Treatment with bromine resulted in oxidative ring opening and elimination with triethylamine provided the compound 240. Once again the E-alkene was the major reaction product of this method.
Scheme 88: Reissig’s Method for the Preparation of α,β-Unsaturated-γ-Keto Esters

In 1994, Hoffman’s research group developed the first chain extension/elimination reaction in which 1,3-dicarbonyl compounds were used to generate 1,4-dicarbonyl compounds (Scheme 89). An unsubstituted β-keto ester 241 was alkylated with α-bromoacetate to offer compound 242. After reacting with (p-nitrophenyl) sulfonyl peroxide (p-NBSP), which resulted in the insertion of the nosyloxy group, trifluoroacetic acid was used to deprotect the t-butyl ester. Decarboxylation provided the 3-(nosyloxy)-4-keto ester 243. Elimination of nosyloxy group with a base provided the α,β-unsaturated-γ-keto esters with selective formation of the E-olefin 244.
Scheme 89: Hoffman's Method for the Preparation of α,β-Unsaturated-γ-Keto Esters

In 2006, Blechert's research group illustrated another method to prepare α,β-unsaturated-γ-ketone macrolides in the total synthesis of antibiotic (-)-A26771B (Scheme 90). The β-keto lactone 245 was generated via a lengthy synthetic sequence. After sodium borohydride reduction and mesylation, elimination with DBU offered compound 246. Deprotection with trifluoroacetic acid and oxidation with TEMPO/ pTSOH produced the hydroxyketone 247. Finally, successful esterification of compound 247 with succinic anhydride offered the final (-)-A26771B 248.
Although methods for the preparation of α,β-unsaturated-1,4-dicarbonyl compounds that would be applicable to macrolide system are available, the development of a general and highly-efficient method to facilitate formation of compounds possessing α,β-unsaturated-γ-hydroxy or α,β-unsaturated-γ-ketone functionality is still needed.

Zercher's research group has successfully developed a convenient, one-pot zinc-mediated chain extension reaction for the preparation of γ-keto carbonyl compounds. Recently, a modification on this reaction was developed to approach α,β-unsaturated-1,4-dicarbonyl compounds. According to the mechanism of the chain extension reaction described earlier (Scheme 10), the zinc organometallic
intermediate 45 is postulated. Oxidation of the intermediate with iodine and treatment with DBU facilitate the formation of α,β-unsaturated-γ-keto carbonyl systems. A series of starting materials with various functional groups was investigated by Ronsheim (Scheme 91). β-Keto esters and β-keto amides were good substrates for this tandem reaction sequence. Even alkene functionality was tolerated well in the reaction with no observed cyclopropanation, as long as carbenoid equivalents and the time of the reaction were controlled. Amino acid derived γ-keto esters and amides were prepared through this zinc-mediated chain extension-oxidation-elimination reaction, which offers an alternative synthetic approach to peptide isostere preparation.

\[
\begin{align*}
\text{R} & \quad \text{O} \\
& \quad \text{O} \quad \text{Et}_2\text{Zn} \\
& \quad \text{or EtZnCH}_2\text{I} \\
\Rightarrow & \quad \text{Et}_2\text{Zn} \quad \text{or EtZnCH}_2\text{I} \\
\Rightarrow & \quad \text{DBU} \quad \text{I}_2 \\
\end{align*}
\]

\[\text{249}\]

\[\text{41} \quad \text{R} \quad \text{R}' \quad \text{O} \quad \text{O} \quad \text{Et}_2\text{Zn} \quad \text{or EtZnCH}_2\text{I} \quad \text{DBU} \quad \text{I}_2 \quad \text{249}\]

1) \[\text{250}\]

2) \[\text{252}\]

3) \[\text{251}\]

4) \[\text{253}\]

Scheme 91: Zercher's Method for the Preparation of α,β-Unsaturated-γ-Keto Carbonyl Compounds

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Moreover, this methodology has been extended to a variety of β-keto macrolides with different ring size and the formal synthesis of (−)-Pyrenophorin. The total synthesis of (−)-Patulolide A and (±)-Patulolide B was also accomplished. The general strategy for macrolide formation is described below (Scheme 92). Diketene was reacted with various unsaturated alcohols to produce β-keto esters. The bis-olefin can be formed by alkylation of the dianion. Ring closing metathesis with Grubbs' first generation catalyst offered the unsaturated β-keto macrolides. Hydrogenation under palladium catalysis reduced the double bonds and generated the precursor for the chain extension-oxidation-elimination reaction. The final products 59A and 59B were formed with variations in the Z/E ratio that depended on the macrolide ring size. When Ronsheim studied the chain extension-oxidation-elimination reaction of 12-membered ring, the 13-membered ring product was formed with excellent E selectivity. Formation of a 13-membered ring with selective formation of an E-alkene is needed for the synthesis of (+)-Brefeldin A.
Since the conversion from 260 to 203 has been successfully reported (Scheme 93) and an efficient method of the formation of α,β-unsaturated-γ-keto macrolides has been developed in the Zercher research group, we decided to undertake a formal synthesis of (+)-Brefeldin A through formation of 260.

Scheme 93: Conversions from 260 to 203

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2. Results and Discussion

a) Initial Model Study towards the Formal Synthesis of (+)-Brefeldin A Using Zinc-Mediated Chain Extension-Oxidation-Elimination Reaction

Since the zinc-mediated chain extension-oxidation-elimination has not been performed on a bicyclic compound with a thirteen-membered ring, a simplified model 261 was designed to investigate the key chain extension-oxidation-elimination before investing a great deal of effort in the total synthesis (Figure 6). We felt that removal of the methyl group from the thirteen-membered ring and the alcohol on the five-membered ring would provide an appropriate model for testing the key steps in the synthetic approach.

![Proposed Model for the Study](image)

Figure 6: Proposed Model for the Study

Retrosynthetic analysis suggested a β-keto macrolide 262 with the E-double bond configuration would be needed for performing the zinc-mediated chain extension-oxidation-elimination reaction. This macrocyclic olefin 262 could be generated from ring-closing metathesis, which would require the β-keto ester 263 starting material. A modified Claisen condensation reaction using the
trans-homoallylic carboxylic acid 264 as the starting material was proposed for the preparation of compound 263 (Scheme 94).

Scheme 94: Retro-synthetic Analysis of the Proposed Model Study towards the Formal Synthesis of (+)-Brefeldin A

Carboxylic acid 264 with desired stereochemistry was unknown in the literature, which indicated that a simple approach to its preparation was needed. Since the trans-homoallylic alcohol 265 was reported in the literature, a suitable oxidation reaction of compound 265 should provide the targeted key intermediate 264 (Scheme 95).

Scheme 95: Attempted Oxidative Preparation of Homoallylic Carboxylic Acid 264
A regioselective cyclization reaction with epoxide opening was applied initially (Scheme 96). The reaction between the lithium salt of compound 267 and the epoxide derivative 268 provided compound 269. After a radical-mediated reaction initiated by AIBN, the epoxy-allylic stannane was obtained in good yield. The cyclization was accomplished by treatment with n-butyllithium at -78 °C to provide the homoallylic alcohol 265.

Scheme 96: Preparation of Compound 265 Using Epoxy-Allylic Stannane Cyclization

A mild, two-step oxidation for the conversion from alcohol 265 to carboxylic acid 264 was used (Scheme 97). Treatment of compound 265 with N-methylmorpholine N-oxide (NMO) with a catalytic amount of
tetra-n-propylammonium perruthenate (TPAP) produced the precursor aldehyde 271, which was oxidized with sodium chlorite in good yield.

\[
\text{Scheme 97: Oxidative Preparation of Compound 264}
\]

Though this synthetic approach to compound 272 was performed successfully, the toxicity of the organostannane compound, modest diastereoselectivity and the use of non-economic reagents like TPAP encouraged the use of another approach, in which the homoallylic ethyl ester 272 was used as the precursor for hydrolysis to prepare compound 264 (Scheme 98).

\[
\text{Scheme 98: Attempted Approach to Compound 264 Using Saponification}
\]

A synthetic route was selected, in which conjugate addition of \( p \)-tolyl \( \alpha \)-lithio-\( \beta \)-(trimethylsilyl) ether sulfoxide and subsequent electrophilic trapping of the resulting enolate reaction product were used to prepare compound 264. Upon
preparation of \((L)\)-menthyl-tolylsulfinate 274,\(^{83}\) a Grignard reagent prepared from methyl iodide was added to offer the optically pure methyl tolylsulfoxide 275. After treatment with \(n\)-butyllithium, the \(\alpha\)-sulfinyl carbanion was generated and reacted with iodomethyl-trimethylsilane to form compound 276 with excellent yield (Scheme 99).\(^{84}\)

\[
\begin{align*}
\text{SOCl}_2 & \quad \text{a) } \text{LDA} \\
\text{Na} & \quad \text{b) } (L)\text{-menthol, pyridine} \\
\text{c) HCl} & \quad \text{Me}_3\text{Si-I} \\
\text{273} & \quad \text{275} \quad \text{276}
\end{align*}
\]

**Scheme 99**: Preparation of \(\beta\)-Tolyl-\(\beta\)-(Trimethylsilyl)ether Sulfoxide 276

The electrophile 279 was prepared in a three-step reaction sequence, previously reported in the literature (Scheme 100).\(^{85}\) A ring-opening reaction between tetrahydrofuran and hydrobromic acid offered the 1-bromo-4-butanol 277. After PCC oxidation, Horner-Emmons reaction provided the targeted electrophile 279 in near quantitative yield.
Conjugate addition of the α-sulfanyl carbanion, generated with lithium diisopropylamide (LDA), to the α,β-unsaturated system generated an enolate, which cyclized to form the five-membered ring in which the two substituents were _trans_. Compound 280 was unstable at room temperature or in an acidic environment. A by-product was formed when the material was left to sit over time. This by-product was determined to be 281, which was formed by elimination of the sulfonyl group (Scheme 101).
Therefore, immediate treatment of 280 with tetrabutylammonium fluoride (TBAF) was necessary to minimize the formation of 281 and provide the homoallylic ethyl ester 272. Saponification of the ester with 3M lithium hydroxide for 8 h produced the targeted homoallylic carboxylic acid 264 in 80% yield (Scheme 102). No α-proton epimerization was observed by NMR analysis.

A Masamune-Brooks reaction was attempted for the preparation of the β-keto ester 263 using 2-((hex-5-enyloxy)carbonyl)acetic acid (Scheme 103). However, this reaction provided very little of the desired β-keto ester. A by-product (282) was formed through self-condensation. Inefficient formation of the sterically hindered acylimidazole appears to be responsible for this poor reactivity. After extending the reaction time between compound 264 and CDI from 10 min to 1 h, the β-keto ester 282 was prepared in a modest yield.
Scheme 103: Attempted Preparation of Compound 263 Using Masamune-Brooks Reaction

Since an efficient modified Claisen condensation reaction was developed by our group for the preparation of series of β-keto imides, similar chemistry was also utilized to prepare compound 263 using hex-5-enyl acetate 283 as the enolate source (Scheme 104). After careful control of enolate formation to avoid self-condensation, the acyl imidazole solution was transferred to the enolate solution by cannula to provide compound 263 in a yield greater than 80% without detectable epimerization.

Scheme 104: Preparation of Compound 263 Using Modified Claisen Condensation
With the successful formation of unsaturated β-keto ester 263, ring closing metathesis (RCM) using Grubbs’ first generation catalyst in the dichloromethane was performed to prepare the unsaturated β-keto macrolide 262 (Scheme 105). A second portion of catalyst was necessary for complete conversion of the reaction that ran overnight at reflux. Two separable macrolides 262A and 262B were detected with $E:Z = 3.5:1$ ratio based on $^1$H NMR and 1D NOE spectra of the crude reaction material.

**Scheme 105: Ring Closing Metathesis (RCM) for the Preparation of Unsaturated β-Keto Macrolide 262**

Attempted iodine-catalyzed double bond isomerization over the course of seven days was unsuccessful for the conversion of compound 262B to compound 262A. However, isomerization of the Z double bond to the E double bond was successfully achieved by using thiophenol in the presence of the radical initiator AIBN (Scheme 106). 

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A zinc-mediated chain extension-oxidation-elimination reaction was performed on compound 262A to give the α,β-unsaturated-γ-keto macrolide 261 (Scheme 107). Though the targeted compound was unable to be purified from the crude reaction mixture due to the small scale of the reaction (0.1 mmol), coupling constant analysis ($J = 16.0$ Hz) of the $^1$H NMR spectrum of the crude reaction material indicated an E-configuration for newly formed double bond. This result suggested that the formal synthesis of (+)-Brefeldin A using this zinc-mediated chain extension-oxidation-elimination method would be possible.
b) Formal Synthesis of (+)-Brefeldin A Using Zinc-Mediated Chain

Extension-Oxidation-Elimination Reaction

Using the successful model study as a guide, retrosynthetic analysis for the formal synthesis of (+)-Brefeldin A was conducted (Scheme 108). An unsaturated β-keto macrolide 284A with E-double bond configuration was needed for performing the zinc-mediated chain extension-oxidation-elimination reaction. Ring-closing metathesis using Grubbs’ first generation catalyst would offer the macrocyclic system 284A, which required access to the β-keto ester 285. A Claisen condensation reaction to generate 285 requires access to the trans-homoallylic carboxylic acid 286, which could be viewed as the key intermediate. A challenging aspect of this approach is the diastereoselective incorporation of a secondary alcohol protected by the methoxymethyl (MOM) group.

![Scheme 108: Retrosynthetic Analysis for the Formal Synthesis of (+)-Brefeldin A](image)

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One method known in the literature to approach the key intermediate 286 involves a highly diastereoselective palladium-catalyzed cyclization as the key step (Scheme 109).\textsuperscript{88} A reaction between epoxide 287 and alkyne anion, generated by treatment with n-butyl lithium was reported to provide compound 288. After reduction with palladium/barium sulfate to provide the Z-alkene, the epoxide 289 was opened using ethyl 2-(phenylsulfonyl)acetate anion. The deprotection of the tetrahydropyranyl group with methanol and p-toluenesulfonic acid resulted in the spontaneous lactonization and formation of compound 290. After carbonate formation with ethyl chloroformate, palladium-catalyzed cyclization in dichloromethane offered the highly diastereomerically-enriched product 292. Removal of the sulfonyl group offered the \textit{trans}-1,2-substituted hydroxycyclopentane 293. For the purpose of a synthetic approach to (+)-Brefeldin A, MOM-protection and saponification with lithium hydroxide should provide the targeted compound 286.
Scheme 109: A Highly Diastereoselective Palladium-Catalyzed Cyclization

In spite of the availability of this literature procedure, the lengthy synthetic route and the toxicity of some reagents inspired the development of an alternate synthetic approach. In the model study described earlier (Scheme 101), the conjugate addition of p-tolyl α-lithio-β-(trimethylsilyl) ether sulfoxide and subsequent electrophilic trapping reaction were successful in generating compound 280 in high yield and high stereoselectivity. Performance of a similar reaction on a substrate in which the
MOM-protected secondary alcohol was introduced (Figure 7) could provide the solution to the preparation of the key intermediate $294$.

![Figure 7: (2S,5E)-Ethyl-6-Bromo-5-(Methoxymethoxy)hex-2-Enoate](image)

A synthetic route using (S)-malic acid $295$ as the starting material was designed to approach compound $294$ (Scheme 110). Though the enantiomerically pure 1,2,4-butanetriol $296$ is commercial available, convenient reduction of (S)-malic acid with borane provided a large supply, which was adequate for the entire study.$^{89}$ Acetal $297$ was prepared using $p$-toluenesulfonic acid as a catalyst. Swern oxidation was adopted instead of PCC oxidation and provided the aldehyde $298$ in a high yield. After Horner-Emmons reaction and hydrolysis of the acetal with 1M hydrochloric acid, the unsaturated 1,2-diol was prepared in overall 80% yield in 3 steps.$^{90}$

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Two different approaches were attempted for the preparation of compound 294. The indirect route used tosylchloride to react with the primary alcohol of the 1,2-diol 300 and provided compound 301. MOM protection of the secondary alcohol was followed by replacement of the tosylate with bromide, which provided the (5S,2E)-ethyl 6-bromo-5-(methoxymethoxy)hex-2-enoate 294. (Scheme 111).
A direct approach to compound 294 was developed in which the primary alcohol was selectively brominated using triphenylphosphine and carbon tetrabromide (Scheme 112). Syringe pump addition of triphenylphosphine was necessary to optimize selective bromination of the primary alcohol. Reaction between compound 303 and methoxymethyl chloride using diisopropylethylamine as the base provided the targeted electrophile 294.
The stereoselective conjugate addition of the α-sulfinyl carbanion, derived from (L)-menthyl-tolylsulfinate and LDA, to compound 294 was studied (Scheme 113). Very encouragingly, only one predominant diastereomer 304 (de >95%) was detected by the $^{13}$C NMR analysis of the crude reaction mixture, although the stereochemistry could not be assigned.

Scheme 113: Formation of Compound 304

The configuration of the newly generated stereocenters was clarified after tetrabutylammonium fluoride (TBAF) induced elimination and lithium aluminum hydride (LAH) reduction of the ester 305 (Scheme 114). After comparing the spectroscopic data to those reported for compound 310, the homoallylic primary alcohol 306 was determined to possess the incorrect stereochemistry.
Since the stereochemistry of the MOM-protected alcohol was determined by the
(S)-malic acid and the formation of the trans-substituted cyclopentane was favored in
the model study, we felt that inversion of both of the two tertiary sp³-centers was
necessary for formation of the desired compound. The method to invert the absolute
configuration at the other two sp³-centers would require use of the alternate
menthol-derived sulfoxide. Stereoselective cyclization through the conjugate addition
of the α-sulfinyl carbanion derived from (D)-menthyl-tolylsulfinate to compound 294
was investigated (Scheme 115). Not surprisingly, only one predominant diastereomer
308 (de >95%) was detected by analysis of the 13C NMR spectrum, although the
stereochemistry could not be assigned. The newly generated stereocenters were
clarified through a procedure similar to that described in Scheme 114. After
comparing the spectroscopic data to the known compound 310, homoallylic primary
alcohol was shown to be the desired compound.

Scheme 114: TBAF Elimination and LAH Reduction on Compound 304
Scheme 115: TBAF Elimination and LAH Reduction on Compound 308

Saponification with 3M lithium hydroxide for eight hours produced the targeted homoallylic carboxylic acid 286 in an excellent yield with no epimerization (Scheme 116). Lithium hydroxide was found to be more suitable than sodium hydroxide for this ester cleavage.

Scheme 116: The Other Approach to Compound 286

With the successful formation of the key intermediate 286, a simple two-step reaction sequence was performed to prepare compound 313, the precursor for the modified Claisen condensation (Scheme 117).\textsuperscript{86} Generation of the cuprate from

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1-bromo-4-butene and addition to (S)-propylene oxide provided an enantiomerically pure alcohol 312, which could be acetylated in almost quantitative yield. After treatment of compound 313 with LDA, a solution of acyl imidazole was transferred to the enolate solution by cannula. Compound 285 was generated in greater than 80% yield without the detectable epimerization.

**Scheme 117: Preparation of Compound 285 Using Modified Claisen Condensation**

After obtaining the unsaturated β-keto ester 285, Grubbs’ first generation catalyst was used to conduct a ring closing metathesis (RCM) and prepare the unsaturated β-keto macrolide 284 (Scheme 118). Dichloromethane proved to be a better solvent than toluene for full conversion of the starting material to the targeted compound 284, although addition of a second portion of catalyst was still necessary during overnight...
reflux. Two macrolides 284A and 284B, separated by column chromatography were formed with $E:Z = 3.5:1$ ratio, as assigned by $^1$H NMR and 1D NOE analysis of the crude reaction mixture. This result was consistent with the model study described above.

![Scheme 118: Ring Closing Metathesis (RCM) for the Preparation of Compound 284](image-url)

In a similar fashion to that observed in the model study, iodine-catalyzed double bond isomerization in the macrocyclic compound was unsuccessful for converting compound 284B to compound 284A. However, isomerization of the $Z$ to the $E$ double bond was accomplished by treatment with thiophenol in the presence of AIBN at 80 °C (Scheme 119).

![Scheme 119: Isomerization of Macrolide Double Bond](image-url)
Before a full investigation of the zinc-mediated chain extension-oxidation-elimination reaction for the preparation of compound 260 was performed, the efficiency of the simple chain extension reaction was studied. Following generation of the zinc-carbenoid (7.5 equiv), the macrolide 284A was added to the solution and allowed to react for 30 min. Although no cyclopropane formation was observed with this excess amount of carbenoid, the zinc-mediated chain extension reaction did not go completion. The reaction time was extended from 30 min to 2 h, but starting material was still observed in the product mixture. The reason for the presence of unreacted starting material is unknown, although the combination of the slow chain extension reaction of β-keto macrocyclic compounds and competitive decomposition of the carbenoid may be responsible. Increasing the equivalents of carbenoid from 7.5 to 10 did result in more efficient chain extension, although an unexpected cyclopropane derivative 315 was detected by analysis of the $^1$H NMR spectrum (Scheme 120). The stereochemistry of the cyclopropane was not assigned.
A modification of the reaction was performed, in which carbenoid (overall 7.5 equiv) was added in two portions (Scheme 121). After treatment of the β-keto macrolide 284A for 30 min with 5 equivalents of carbenoid prepared in advance, a second portion of diethyl zinc and 1,1-diiodomethane (2.5 equiv) was added sequentially. After an additional thirty minutes of reaction time, complete conversion of the chain extended product 314 was accomplished.
These conditions were repeated and iodine (8 equiv) was added to the solution to trap the chain extension intermediate (Scheme 122). However, after elimination of iodide by treatment with DBU, only a trace of the targeted α,β-unsaturated-γ-keto-macrolide was produced. The major product was the simple chain extension product 314.

\[
\begin{align*}
\text{Scheme 122: Attempted Oxidation-Elimination Reaction of Compound 316}
\end{align*}
\]

Extending the reaction time between the iodine and the zinc-organometallic from 1 min to 30 min did not increase the ratio of the targeted compound 260. However, an increase in the amount of cyclopropane product was observed (Scheme 113).

\[
\begin{align*}
\text{Scheme 123: Attempted Oxidation-Elimination Reaction of Compound 316}
\end{align*}
\]
Eventually, increasing the equivalents of iodine from eight to fourteen and shortening the reaction time (to avoid the cyclopropane by-product formation) provided the targeted compound 260 (Scheme 124). The newly formed double bond, generated from the zinc-mediated chain extension-oxidation-elimination reaction, was assigned the E-configuration based on $^1$H-$^1$H coupling constant ($J = 15.0$ Hz), as well as through comparison to the known literature data. The spectroscopic data of the material in the chain extension-oxidation-elimination sequence was identical to that report in the literature. Therefore, the successful preparation of 260 completed the formal synthesis of (+)-Brefeldin A.

Scheme 124: Successful Zinc-Mediated Chain Extension-Oxidation-Elimination Reaction on Macrolide 284A

Overall, the successful formal synthesis of (+)-Brefeldin A using zinc-mediated chain extension-oxidation-elimination reaction as a key step represents the shortest synthetic route to (+)-Brefeldin A reported to date. This accomplishment illustrates the power and utility of the zinc-mediated chain extension reaction.
CHAPTER III

ZINC-MEDIATED CHAIN EXTENSION REACTIONS WITH SUBSTITUTED CARBENOIDS

1. Introduction to β-Substituted-γ-Keto Carbonyl Compounds

As discussed in Chapter 1, variations in the tandem zinc-mediated chain extension reaction developed by Zercher’s research group have successfully facilitated the regio- and stereoselective insertion of α-substituents into 1,4-dicarbonyl compounds. In order to extend the scope of this practical method, a new variant of the zinc-mediated chain extension was proposed which would allow the generation of β-substituted-γ-keto carbonyl compounds using substituted carbenoids.

Literature reports have described efforts to selectively alkylate 1,4-dicarbonyl systems. However, unsatisfactory regioselectivity and multiple-alkylations are frequently observed. A hypothetical example is illustrated below (Scheme 125). Treatment of a 1,4-dicarbonyl compound 317 with base to generate an enolate and the reaction of this enolate with alkyl halide could generate a number of potential monoalkylation products, like 318, 319, 320, due to small pKa difference of various α-protons. Regioselective control is further complicated by the potential for multiple
alkylation. Furthermore, aryl incorporation at an α-position is quite challenging using these classical reaction conditions. The difficulty in performing these reactions suggests that a method which facilitates the regiospecific incorporation of a β-substituent into 1,4-dicarbonyl compounds would be useful. A number of approaches have been developed for this purpose. Some of these methods are described below.

Scheme 125: Alkylation of 1,4-Dicarbonyl Compounds

In 1991, Kulkarni’s research group used the well-known sequentially Claisen rearrangement and Wacker oxidation to generate the β-methyl-γ-keto esters (Scheme 126). Heating but-3-en-2-ol 322 and triethylorthoacetate to 140 °C produced the γ,δ-unsaturated ester 323 through a Claisen rearrangement. Wacker oxidation of 323 in aqueous dimethoxyethane at 80 °C provides the β-methyl-γ-keto ester 324.
In 1993, Kohno’s research group developed a radical-initiated reaction for the formation of β-alkyl-γ-keto amides (Scheme 127). After the oxidation of α-tributylstannyl amide 325 with tetrabutylammonium hexanitratocerium (IV), the α-radical intermediate 326 reacts with a silyl enol ether to provide the β-alkyl-γ-radical intermediate 327. One electron oxidation of 327 from additional Ce (IV) and loss of the silyl group produces the targeted β-alkyl-γ-keto amides 328. One drawback for this methodology is that the oxidation reaction requires the presence of a benzylalkoxy radical, which limits the application of this method to specific substrates.
Scheme 127: Kohno’s Method for the Preparation of β-Alkyl-γ-Keto Amides

In 2000, Satoh’s research group reported another method for β-alkyl-γ-keto amide preparation (Scheme 128). Reacting 3-iodobutyramide 329 with activated zinc provided zinc-homoenolate 330. Acylation with benzoyl chloride derivatives in the presence of palladium (0) produced the desired β-methyl-γ-keto amides 331 in good to excellent yields.

Scheme 128: Satoh’s Method for the Preparation of β-Methyl-γ-Keto Amides

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Recently, Kashima’s research group published a variation on a traditional alkylation approach to \( \beta \)-substituted-\( \gamma \)-keto esters (Scheme 129).\(^7\) The reaction between the lithium enolate of an acylated-3,5-dimethylpyrazole 332 and \( \alpha \)-bromoacetate esters generated a 3-substituted-4-(3,5-dimethylpyrazol-1-yl)-4-oxobutanoic esters 333. Subsequent reaction of 333 with a Grignard reagent affords the \( \beta \)-substituted-\( \gamma \)-keto esters 334.

![Scheme 129: Kashima’s Method for the Preparation of \( \beta \)-Alkyl-\( \gamma \)-Keto Esters](image)

Moreover, 3-phenyl-\( l \)-menthopyrazole was shown to be a good chiral auxiliary for the enantioselective synthesis of \( \beta \)-substituted-\( \gamma \)-keto esters following the identical synthetic route described above. The chiral auxiliary can be almost fully recovered without detectable racemization (Scheme 130). The ratio of enantiomers was quantified by a HPLC study and the absolute configuration of targeted products was characterized by optical rotation. However, the efficiency of the replacement of the...
chiral auxiliary with the Grignard reagent was diminished with the increasing steric bulk of the auxiliary.

![Chemical structure](image)

Scheme 130: Kashima's Method for the Stereoselective Preparation of $\beta$-Alkyl-$\gamma$-Keto Esters

Though some facile methods have been developed to generate $\beta$-alkyl-$\gamma$-keto carbonyl compounds, most methods possess limitations, such as high reaction temperature, specific functional group requirements, and inefficient reactions due to steric effects. The availability of a simple, high-yielding method to generate the desired $\beta$-substituted-$\gamma$-keto esters from easily accessible starting materials would be desirable.
2. Results and Discussion

a) Initial Study towards Preparation of β-Substituted-γ-Keto Esters

A facile zinc carbenoid-mediated chain extension method for conversion of β-keto carbonyl compounds to γ-keto carbonyl compounds has been developed, in which the carbenoid is generated from diethyl zinc and diiodomethane. The proposed mechanism is illustrated below, which suggests that substituted carbenoid derivatives should serve to incorporate substituted methylene units during the conversion of β-keto carbonyl compounds to γ-keto carbonyl compounds (Scheme 131). Treatment of β-keto carbonyl compounds 41 with diethyl zinc produces an enolate that could trap a carbenoid derived from diethyl zinc and a diidoalkane. The substituted cyclopropane intermediate 339 could be formed through intramolecular cyclization. Release of the three-membered ring's strain would result in formation of β-substituted-γ-keto carbonyl systems. Furthermore, trapping this β-substituted zinc-mediated chain extension reaction intermediate 340 with various electrophiles would generate more complex derivatives. While the stereochemistry at the α-position is established during the reaction between the zinc enolate and the electrophile, the stereochemistry of the β-substituent would be formed in the cyclopropanation process.
Scheme 131: Proposed Mechanism for the Zinc-Mediated Chain Extension Reaction with Substituted Carbenoid

The preparation of $\beta$-substituted-$\gamma$-keto esters through the chain extension of $\beta$-keto esters requires a substituted carbenoid, which can be prepared through the reaction of a 1,1-diiodoalkane with diethylzinc. The most common zinc-carbenoid, besides 1,1-diiodomethane, is derived from 1,1-diiodoethane, which has been used successfully in carbenoid-mediated cyclopropanation reactions.\(^98\)

Several methods are reported in the literature for the preparation of 1,1-diiodoethane.\(^99,101\) One common method, reported by Kammeyer and coworkers, involves reacting iodoethane with 1,1-dichloroethane in the presence of catalytic
anhydrous aluminum chloride (Scheme 132). A modest yield of 1,1-diiodoethane is formed using this method. Purification involves vacuum distillation, in which the volatile byproducts are easily separated from the high boiling diiodoethane. The targeted compound 344 must be stored in the dark using copper wire as a stabilizer.

\[ \text{Cl} \quad + \quad \text{I} \quad \xrightarrow{\text{AlCl}_3 \text{(cat.)}} \quad \text{I} \quad + \quad \text{Cl} \]

Scheme 132: Aluminum Chloride Catalyzed Preparation of 1,1-Diiodoethane

With the precursor 1,1-diiodoethane 344 prepared, the zinc-mediated chain extension reaction was performed on a series of the β-keto esters, which were either commercially available or easily prepared from a reaction between an alcohol and diketene. However, the chain extension reaction was not successful when the carbenoid was generated prior to addition of the β-keto esters (Scheme 133). Using these standard conditions, the β-keto ester starting materials were recovered. The reason for the lack of reactivity was attributed to the absence of enolate formation.

\[ \text{CH}_3\text{CH}_2 \quad + \quad \text{Et}_2\text{Zn} \quad \xrightarrow{\text{R}-\text{O}^\ominus} \quad \text{R} \quad \text{O} \quad \text{R'} \]

Scheme 133: Attempted Preparation of β-Methyl-γ-Keto Esters

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However, after treatment of the β-keto esters with five equivalents of diethyl zinc for ten minutes at 0 ºC to facilitate the enolate formation (Scheme 134), addition of five equivalents of 1,1-diiodoethane provided the targeted β-methyl-γ-keto esters in good to excellent yield in thirty minutes at room temperature (Table 1).

![Scheme 134: Successful Preparation of β-Methyl-γ-Keto Esters](image-url)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Me</td>
<td>Me</td>
<td>76 %</td>
</tr>
<tr>
<td>B</td>
<td>t-Butyl</td>
<td>Me</td>
<td>82 %</td>
</tr>
<tr>
<td>C</td>
<td>Ph</td>
<td>Et</td>
<td>84 %</td>
</tr>
<tr>
<td>D</td>
<td>Me</td>
<td>Bn</td>
<td>80 %</td>
</tr>
<tr>
<td>E</td>
<td>Me</td>
<td>t-Butyl</td>
<td>88 %</td>
</tr>
</tbody>
</table>

Table 1: Conversion of β-Keto Esters to β-Methyl-γ-Keto Esters

A by-product, 2-iodobutane, was always observed in this zinc-mediated chain extension reaction process. This by-product has been reported in the earlier study of cyclopropanation reaction involving the zinc-carbenoid generated from 1,1-diiodoethane. It was not clear whether 2-iodobutane is formed as a result of
carbenoid decomposition or whether it is a by-product of the reaction between 1,1-diiodoethane and diethylzinc.

The same reaction conditions were also used to chain-extend compound 348, which was derived from allyl alcohol and diketene. Although no cyclopropane formation was observed when using an excess amount of carbenoid, the zinc-mediated chain extension reaction did not go to completion within 30 min (Scheme 135). The ratio of starting material (348) to product (349) was 3:1. Extending the reaction time from 30 min to 2 h and increasing the equivalents of carbenoid from 5.0 to 7.5 did not improve the ratio of starting material to product.

\[
\begin{array}{c}
\text{348} \\
\text{O} \quad \text{O} \\
\text{\textbf{a) Et}_2\text{Zn (5 equiv), CH}_2\text{Cl}_2)} \\
\text{\textbf{b) CH}_3\text{CH}_2 (5 equiv)}}
\end{array}
\rightarrow
\begin{array}{c}
\text{349} \\
\text{\textbf{O}} \quad \text{\textbf{O}} \\
\text{348}
\end{array}
\]

Scheme 135: Attempted Preparation of β-Methyl-γ-Keto Allyl Ester 349

The carbenoid addition (overall 7.5 equiv) protocol was modified, based on the assumption that the carbenoid was undergoing decomposition. The detailed procedure was as follows (Scheme 136). The β-keto allyl ester 348 was treated with five equiv
of diethyl zinc for ten minutes at 0 °C to facilitate enolate formation, at which point five equiv of 1,1-diiodoethane were added. After the reaction was allowed to proceed at room temperature for 30 min, a second portion of diethyl zinc and 1,1-diiodoethane (2.5 equiv each) was added sequentially. After an additional 30 min, no starting material was present and the targeted β-methyl-γ-keto allyl ester was isolated in 74% yield.

\[
\begin{align*}
\text{348} & \quad \xrightarrow{\text{a) } \text{Et}_2\text{Zn (5 equiv), CH}_2\text{Cl}_2} \quad \text{349} \\
\text{349} & \quad \xrightarrow{\text{b) } \text{CH}_3\text{CHI}_2 (5 \text{ equiv})} \quad \text{CH}_3\text{CHI}_2 (2.5 \text{ equiv})
\end{align*}
\]

Scheme 136: Successful Preparation of β-Methyl-γ-Keto Allyl Ester 349 with Modified Procedure

Another member of the research group, Rob McGinness, studied the zinc-mediated chain extension reaction with the carbenoid derived from diethyl zinc and 1,1-diiodoethane on a series of β-keto tertiary amides (Scheme 137). Modest yields and the continued presence of starting material were often observed (Table 2). The modified procedure involving two additions of carbenoid did not improve the conversion significantly.\textsuperscript{101}
Scheme 137: Preparation of β-Methyl-γ-Keto Amides

Table 2: Conversion of β-Keto Esters to β-Methyl-γ-Keto Amides

A more disappointing result was observed when a secondary β-keto amide was used as the starting material. An unidentified mixture of products was detected after the zinc-mediated chain extension reaction was performed with carbenoid derived from 1,1-diiodoethane and diethyl zinc (Scheme 138). The reason for this complexity might be due to the secondary amide’s acidic proton.
Since the insertion of a β-methyl group during the chain extension process was successful on the β-keto esters and tertiary amides, another variation was also explored in which 1,1-diiodotoluene 355 was used as the carbenoid source. The aluminum chloride-catalyzed method used for the preparation of 1,1-diiodoethane cannot be applied to the preparation of compound 355 because of the possible Friedel-Crafts reaction. 1,1-Diiodotoluene can be prepared by the reaction of hydrazones with iodine; however, the more convenient and high yielding preparation involving a reaction between trimethylsilyliodide and benzaldehyde was chosen (Scheme 139). 1,1-Diiodotoluene and hexamethyldisiloxane 356 are the products of this reaction. The targeted solid 355 was isolated in greater than 50% yield by vacuum sublimation.

Scheme 138: Attempted Preparation of β-Methyl-γ-Keto Secondary Amide
Scheme 139: Preparation of 1,1-Diodotoluene Using Benzaldehyde and Trimethylsilyl Iodide

With 1,1-diodotoluene prepared, the zinc-mediated chain extension reaction was performed on three β-keto esters using the identical procedure described for 1,1-diiodoethane (Scheme 140). The results listed in Table 3 suggest that with increasing steric size of the R and R’ groups, a decreased yield of the chain extension product was observed. When the starting material was the sterically hindered 4,4-dimethyl-3-oxopentanoate, no chain extension product was detected.
Scheme 140: Preparation of β-Phenyl-γ-Keto Esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Me</td>
<td>Me</td>
<td>74 %</td>
</tr>
<tr>
<td>B</td>
<td>Me</td>
<td>t-Butyl</td>
<td>44 %</td>
</tr>
<tr>
<td>C</td>
<td>t-Butyl</td>
<td>t-Butyl</td>
<td>Unpurified mixture</td>
</tr>
</tbody>
</table>

Table 3: Conversion of β-Keto Esters to β-Phenyl-γ-Keto Esters

b) Initial Study towards Enantioselective Preparation of β-Substituted-1,4-dicarbonyl Compounds

An enantioselective β-methyl insertion during the zinc-mediated chain extension reaction with carbenoid was also attempted. Since the stereochemistry of the β-substituent is determined in the formation of donor-acceptor cyclopropane, the exploration of enantioselective cyclopropanation methods appeared attractive. Denmark’s research group reported the catalytic, enantioselective cyclopropanation of allylic alcohols using the N,N-bis(methanesulfonyl) derivative of (R,R)-1,2-diamino-cyclohexane (Scheme 141).104

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Scheme 141: Enantioselective Cyclopropanation of Allylic Alcohols Using

\[ \text{Et}_2\text{Zn, CH}_2\text{I}_2, \text{CH}_2\text{Cl}_2 \]

\[ \begin{align*}
&\text{358} \\
&\text{359}
\end{align*} \]

\[ \begin{align*}
\text{Me} \\
\text{O=S=O} \\
\text{NH} \\
\text{Me}
\end{align*} \]

\[ \text{(0.1 equiv)} \]

\[ \text{360} \]

(N,N-Bis(methanesulfonyl) Derivative)

(RR)-1,2-Diaminocyclohexane was accessed via resolution of the racemates (Scheme 142). After racemic diaminocyclohexane reacted with (L)-tartaric acid, one diastereomer 362 precipitated selectively. Neutralization of the precipitate with sodium hydroxide provided the enantiomerically pure 361A. Compound 364 was prepared through acylation of compound 361A with butanesulfonyl chloride using triethylamine as a base. Butanesulfonyl chloride was used instead of methanesulfonyl chloride due to the improved solubility of the chiral ligand in the enantioselective cyclopropanation reaction.
Scheme 142: Preparation of $N,N$-Bis(butanesulfonyl) Derivative 364

The zinc-mediated chain extension reaction with carbenoid derived from diethylzinc and 1,1-diiodoethane was performed using a catalytic amount of the bis-sulfonamide derivative 364 for the enantioselective $\beta$-methyl insertion. The $N,N$-bis(butanesulfonyl) derivative 364 was added after deprotonation of the $\beta$-keto ester 347A with diethylzinc. The addition of 1,1-diiodoethane then followed. The chain extension reaction proceeded successfully with full conversion of starting material to the targeted compound 346A. However, the optical rotation measurement of product 346A was zero, which indicated no preference for the synthesis of one enantiomer over the other (Scheme 143). The identification of other suitable chiral ligands for zinc might provide a solution for the enantioselective synthesis of $\beta$-methyl-$\gamma$-keto esters in the future.

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Scheme 143: Attempted Enantioselective Synthesis of β-Methyl-γ-Keto Esters

An Evans chiral auxiliary has been used to control the stereochemistry in the zinc-mediated chain extension-aldol reaction when carbenoid derived from diethylzinc and methylene iodide was used. In that case, no stereocenter is generated at the β-carbon; however, we felt the potential for controlling stereochemistry at the β-carbon through an Evans auxiliary needed to be investigated. The chain extension reaction involving the chiral β-keto imide and carbenoid derived from diethylzinc and 1,1-diiodoethane were investigated (Scheme 144). Two diastereomers in a 1:1 ratio (based on the $^1$H NMR spectrum of the crude reaction mixture) were obtained, which excluded the possibility of diastereoselective β-methyl insertion using an Evans chiral auxiliary.
Scheme 144: Attempted Diastereoselective Synthesis of β-Methyl-γ-Keto Imides

In summary, the zinc-mediated chain extension reaction using carbenoids derived from 1,1-diiodoethane and 1,1-diiodotoluene were successfully developed. This modification facilitates the incorporation of β-substituents and thereby complements the tandem reaction strategy which facilitates α-substitution. Controlling the stereochemistry at the β-position and the development of tandem reaction strategies in which both α and β-substituents are incorporated are under development.
CHAPTER IV

EXPERIMENTAL SECTION

1. General Experimental

Unless otherwise noted, all reactions were run in oven-dried glassware and stirred with teflon-coated magnetic stir-bars. The terms concentrated in vacuo or under reduced pressure refer to the use of a rotary-evaporator or vacuum pump.

a) Solvents

Methylene chloride (CH₂Cl₂), tetrahydrofuran (THF), acetonitrile (CH₃CN), toluene, diethylether (Et₂O), N,N-dimethylformamide (DMF) and methanol were dried by passing through a column using an Inovative Technology Inc. solvent delivery system. Methylene iodide was purchased and copper was added as a stabilizer. Ethyl acetate (EtOAc) was purchased from Pharmco and distilled prior to use. Hexanes were purchased from Pharmco and distilled prior to use. Benzene was distilled from calcium hydride prior to use.

b) Chromatography

Chiral HPLC analysis was performed with a Daicel Chiralpak® AD-RH reverse phase column. Thin Layer Chromatography (TLC) was carried out on EM Science
F254 glass plates and visualized by UV and anisaldehyde or KMnO₄ stains. Column chromatography was performed with Sorbent Technologies flash silica gel (32-63μm). Mobile phases were used as noted.

c) Spectroscopy

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. High Resolution Mass Spectroscopy was performed at Merck Pharmaceutical Co. Optical rotations were conducted using a Rudolf Research Autopol III automatic polarimeter in specified solution and concentrations are given in g/mL. Infrared spectroscopy was performed on a Nicolet 205 Fourier Transform spectrometer. Nuclear Magnetic Resonance (NMR) spectroscopy was performed on Varian Mercury operating at 399.768 MHz for ¹H nuclei and 100.522 MHz for ¹³C nuclei, and Varian Inova operating at 499.766 MHz for ¹H nuclei and 125.679 MHz for ¹³C nuclei. All ¹³C are ¹H-decoupled. Unless otherwise noted, all NMR experiments were carried out in deuterochloroform (CDCl₃) solvent purchased from Cambridge Isotope Laboratory and stored over 4 Å sieves. All chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane (TMS) internal standard.
d) Reagents

Diethylzinc was purchased both as a solution (1.0 M in hexanes) and neat.
Methylene iodide (CH$_2$I$_2$) was purchased from Lancaster chemical companies.
Non-oxidized copper wire was added as a stabilizer. Iodine was sublimed prior to use.
Palladium 10% on carbon was purchased from Aldrich Chemical Co. and used without purification. Bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride (Grubbs’ 1st catalyst) was purchased from Strem Chemical Co. and used without further purification.

2. Preparation of Peptide Isostere

a) Preparation of Peptide Isostere through $N$-Terminus

(S)-Methyl 1-(3-oxobutanoyl)pyrrolidine-2-carboxylate 55

A 250-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with proline methyl ester hydrochloride salt (10 g, 60 mmol), benzene (100 mL), sodium bicarbonate (16.8 g, 200 mmol) and diketene (8.4 mL, 100 mmol) in the indicated order. The suspension was stirred overnight at room temperature. The resulting liquid was filtered through filter paper and ethyl acetate (100 mL) was added to the filtrate. The organic solution was washed with 1 M HCl (50 mL), brine (50 mL), saturated sodium bicarbonate solution (50 mL), and brine (50 mL). The solution was concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl

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acetate = 3:1, \( R_f = 0.10 \) to offer 10.1 g (79%) of 55 as a yellow oily mixture of two rotamers in a 6:1 ratio, with some minor enol forms present. Major rotamer: \(^1\)H NMR (400 MHz, \text{CDCl}_3) \( \delta \) 4.40 (dd, 1H, \( J = 3.9, 6.1 \) Hz), 3.62 (s, 3H), 3.54-3.27 (m, 4H), 2.19 (s, 3H), 2.18-1.81 (m, 4H); \(^1^3\)C (125 MHz, \text{CDCl}_3) \( \delta \) 201.8, 172.1, 165.1, 88.4, 58.5, 51.9, 50.9, 47.4, 29.0, 24.5. Resonances observed for the minor rotamer: \(^1\)H NMR (400 MHz, \text{CDCl}_3) \( \delta \) 4.34 (dd, 1H, \( J = 2.5, 8.4 \) Hz), 3.40 (s, 3H), 2.17 (s, 3H); \(^1^3\)C NMR (125 MHz, \text{CDCl}_3) \( \delta \) 201.8, 174.8, 170.2, 58.3, 51.6, 46.8, 30.3, 24.7, 22.8.

Resonances observed for the enol forms: \(^1\)H NMR (400 MHz, \text{CDCl}_3) \( \delta \) 4.94 (s, 1H), 1.84 (s, 3H). IR (neat, cm\(^{-1}\)): 2900-2700, 1750-1700, 1650, 1230-1140.

**(S)-Methyl 1-(4-oxopentanoyl)pyrrolidine-2-carboxylate 56**

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 40 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 15.0 mL, 15.0 mmol). The solution was cooled to 0 °C and methylene iodide (1.2 mL, 15.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 55 (0.64 g, 3.0 mmol, in 3 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. After TLC analysis (hexanes:ethyl acetate = 3:1; \( R_f = 0.10 \)) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (25 mL). The mixture was extracted with diethyl ether (2 x 30 mL), washed with brine (25 mL), and

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dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 1.5:1, Rf = 0.20) to yield 0.52 g (76%) of 56 as a colorless oily mixture of two rotamers in a 4:1 ratio. [α]D25 = -39.1 (c = 0.033 g/mL, CHCl3).

Major rotamer: 1H NMR (400 MHz, CDCl3) δ 4.35 (dd, 1H, J = 3.9, 8.6 Hz), 3.62 (s, 3H), 3.59-3.45 (m, 2H), 2.87-2.37 (m, 4H), 2.10 (s, 3H), 2.20-1.78 (m, 4H); 13C (100 MHz, CDCl3) δ: 207.4, 172.6, 170.2, 58.4, 51.9, 46.6, 37.4, 29.8, 29.0, 27.9, 24.5.

Resonances observed for the minor rotamer: 1H NMR (400 MHz, CDCl3) δ 4.45 (dd, 1H, J = 2.6, 8.6 Hz), 3.67 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 172.4, 170.5, 59.1, 52.3, 46.2, 37.8, 31.1, 22.3. IR (neat, cm⁻¹): 3350-3250, 2900-2700, 1750-1700, 1650, 1230-1140.

(S)-Methyl 1-((S)-2-((S)-methoxy(phenyl)methyl)-4-oxopentanoyl)pyrrolidine-2-carboxylate 59

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 10 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 2 mL, 2.0 mmol). The solution was cooled to 0 °C and methylene iodide (0.16 mL, 2.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 58 (0.33 g, 1.0 mmol, in 1 mL of methylene chloride) was added by syringe to the resulting white suspension. The
mixture was stirred for 30 minutes. After TLC analysis (hexanes:ethyl acetate = 1:1, \( R_f = 0.25 \)) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (2 x 10 mL), washed with brine (15 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 1:1, \( R_f = 0.30 \)) to yield 0.17 g (50%) of 59 as a yellow oily mixture of two rotamers in a 4:1 ratio. (NMR spectrum available in the CD)

(S)-Methyl 1-((2S,3S,5S)-5-hydroxy-5-methyl-2-phenyltetrahydrofuran-3-carbonyl)pyrrolidine-2-carboxylate 62

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 10 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C and methylene iodide (0.20 mL, 2.5 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 55 (0.22 g, 1.0 mmol, in 2 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes, at which time freshly distilled benzaldehyde (0.13 g, 1.2 mmol) was added into the reaction mixture by syringe. After TLC analysis (hexanes:ethyl acetate = 1.5:1, \( R_f = 0.20 \)) indicated the chain extension intermediate...
was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (10 mL). The mixture was extracted with diethyl ether (2 x 15 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous sodium sulfate. The organic solution was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 1:1, \( R_f = 0.25 \)) to yield 0.23 g (70%) of 62 as white crystals (mp: 113-115 °C) in which one major hemiacetal form is present. \([\alpha]^{25}_D = -11.6 \) (c = 0.011 g/mL, CHCl₃).

\( ^1H \) NMR (500 MHz, CDCl₃) \( \delta \) 7.41-7.26 (m, 5H), 6.65 (s, 1H), 5.18 (d, 1H, \( J = 5.0 \) Hz), 4.56 (dd, 1H, \( J = 3.5, 8.6 \) Hz), 3.80 (s, 3H), 3.38-3.23 (m, 3H), 2.31-1.84 (m, 6H), 1.69 (s, 3H); \( ^{13}C \) NMR (125 MHz, CDCl₃) \( \delta \) 174.8, 171.9, 142.0, 128.5, 127.8, 125.4, 105.3, 83.2, 58.8, 52.2, 51.0, 47.6, 41.6, 28.9, 24.9, 24.3. The presence of the open chain form as a minor constituent is confirmed by the \( ^{13}C \) resonance of 207.7. IR (neat, cm\(^{-1}\)) : 3400 (b, OH), 2956, 1744, 1640, 1448.

(2S)-Methyl

1-((2S,3S)-5-methyl-2-phenyltetrahydrofuran-3-carbonyl)pyrrolidine-2-carboxylate 63A and 63B

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (10 mL), compound 62 (0.43 g, 1.3 mmol). After the solution was cooled to the -78 °C, triethylsilane (0.86 mL, 5.2 mmol) and boron trifluoride diethyl etherate (0.52 mL, 5.2
mmol) were added dropwise in the indicated order. The reaction solution was left stirring for forty minutes at -78 °C and twenty-one hours at room temperature. The solution was quenched with saturated sodium bicarbonate solution (10 mL), extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous sodium sulfate and concentrated in vacuo. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 2:1, \( R_f = 0.20 \)) to offer 0.29 g (70%) of 63A and 63B as a yellow oily mixture of two isomers in a 4.4:1 ratio. Resonance observed for the major isomer 63A: \( ^1H \) NMR (500 MHz, CDCl\(_3\) ) \( \delta 7.48-7.25 \) (m, 5H), 4.97 (d, 1H, \( J = 7.9 \) Hz), 4.45 (dd, 1H, \( J = 4.2, 8.6 \) Hz), 4.32 (m, 1H), 3.75 (s, 3H), 3.22 (m, 1H), 3.04 (m, 1H), 2.88 (m, 1H), 2.48 (m, 1H), 2.10 (m, 1H), 1.96-1.71 (m, 3H), 1.38 (d, 1H, \( J = 6.2 \) Hz), 1.24 (d, 3H, \( J = 6.1 \) Hz), 1.18 (m, 1H); \( ^{13}C \) (100 MHz, CDCl\(_3\) ) \( \delta 170.0, 169.4, 138.8, 125.9, 125.3, 123.5, 82.2, 73.3, 56.4, 49.7, 49.4, 44.4, 36.0, 26.6, 22.2, 18.6. Resonances observed for the minor isomer 63B: \( ^1H \) NMR (500 MHz, CDCl\(_3\) ) \( \delta 4.97 \) (d, 1H, \( J = 8.5 \) Hz), 4.46 (dd, 1H, \( J = 3.7, 8.1 \) Hz), 3.69 (s, 3H), 1.36 (d, 3H, \( J = 6.1 \) Hz); \( ^{13}C \) NMR (100 MHz, CDCl\(_3\) ) \( \delta 170.0, 169.2, 138.3, 126.1, 124.4, 123.1, 82.6, 73.2, 56.4, 50.1, 49.4, 44.0, 36.0, 28.5, 20.0, 18.9.  

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(S)-Methyl

1-((S)-2-((S)-(methylthiocarbonothioyloxy)(phenyl)methyl)-4-oxopentanoyl)pyrrolidine-2-carboxylate 68

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with sodium hydride (24 mg, 0.6 mmol, 60% in the mineral oil). Hexanes (2 mL) was added to the flask to wash the sodium hydride. The hexane was removed by syringe, and then tetrahydrofuran (4 mL) was added by syringe. The solution was cooled to 0 °C and carbon disulfide (76 mg, 1.0 mmol) was added by syringe. After stirring for 5 minutes, compound 62 (0.10 g, 0.3 mmol, in 1 mL of tetrahydrofuran) was added by syringe, followed by methyl iodide (0.14 mg, 1.0 mmol). After TLC analysis (hexanes:ethyl acetate = 1:1, Rf = 0.25) indicated 62 was consumed, the solution was quenched with saturated aqueous ammonium chloride (3 mL). The solution was extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 1.5:1, Rf = 0.20) to yield 96 mg (74%) of 68 as a yellow oily mixture of two rotamers in a 3.3:1 ratio, [α]25D = +15 (c = 0.004 g/mL, CHCl3). Major rotamer: 1H NMR (500 MHz, CDCl3) δ 7.37-7.27 (m, 5H), 6.59 (d, 1H, J = 9.0 Hz), 4.31 (dd, 1H, J = 4.4, 8.4 Hz), 3.77-3.64 (m, 2H), 3.64 (s, 3H), 3.22 (dd, 1H, J = 10.3, 18.3 Hz), 2.92 (m, 1H), 2.79 (dd, 1H, J = 2.9, 18.3 Hz), 2.55 (s, 3H), 2.14 (s, 3H), 2.06 (m, 1H), 1.88-1.73 (m,
3H); $^{13}$C (125 MHz, CDCl$_3$) δ 214.1, 207.2, 172.2, 169.8, 137.0, 128.5, 128.4, 127.4, 84.1, 59.2, 51.9, 47.0, 45.4, 43.6, 30.1, 29.2, 24.8, 19.2. Resonances observed for the minor rotamer: $^1$H NMR (500 MHz, CDCl$_3$) δ 6.51 (d, 1H, $J$ = 10.0 Hz), 3.84 (d, 1H, $J$ = 8.6 Hz), 3.77 (s, 3H), 2.53 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 214.4, 205.7, 172.3, 169.7, 137.4, 128.5, 126.8, 85.0, 59.1, 52.3, 46.1, 45.8, 43.5, 30.6, 30.2, 22.1, 19.2. IR (neat, cm$^{-1}$): 2954-2852, 1740, 1715, 1640, 1436, 1202.

(5)-Methyl 1-((R)-2-benzyl-4-oxopentanoyl)pyrrolidine-2-carboxylate 69

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with toluene (4 mL). Compound 68 (0.16 mg, 0.4 mmol), tributyl tinhydride (0.16 mL, 0.6 mmol) and AIBN (10 mg, 0.06 mmol) were added sequentially to the flask. The solution was heated to 80 °C for eight hours. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 1:1, $R_f$ = 0.11) to give 88 mg (69%) of 69. [α]$^2$$_D$ = +3.8 (c = 0.002 g/mL, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.32-7.18 (m, 5H), 4.46 (dd, 1H, $J$ = 4.7, 8.9 Hz), 3.81 (m, 1H), 3.73 (s, 3H), 3.40 (m, 1H), 3.20 (m, 1H), 3.12-3.00 (m, 2H), 2.59 (dd, 1H, $J$ = 8.8, 13.7 Hz), 2.38 (dd, 1H, $J$ = 3.2, 18.0 Hz), 2.18 (m, 1H), 2.06 (s, 3H), 2.06-1.92 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.8, 173.4, 172.7, 138.7, 129.1, 128.4, 126.4, 58.7, 52.0, 46.8, 45.1, 40.6, 37.7, 29.9, 29.1, 24.8. IR (neat, cm$^{-1}$): 2923-2851, 1744, 1713, 1634, 1436, 1365.
(S)-Methyl 1-(S)-2-(hydroxymethyl)-4-oxopentanoyl)pyrrolidine-2-carboxylate

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 35 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 15.0 mL, 15.0 mmol). The solution was cooled to 0 °C and methylene iodide (1.20 mL, 15.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 55 (0.64 g, 3.0 mmol, in 3 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. Paraformaldehyde (0.5 g) was placed in a dry one-necked round-bottomed flask, which was capped with a rubber septum. One end of a cannula was inserted through the septum in the flask that contained paraformaldehyde, and the other end of the cannula was inserted through the septum in the flask that contained the zinc reagent. The paraformaldehyde flask was heated with a heat gun to induce formation of formaldehyde, which was bubbled into the zinc-carbenoid solution for 10 minutes. After TLC analysis (hexanes:ethyl acetate = 1.5:1, Rf = 0.20) indicated the chain extension intermediate was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (15 mL). The solution was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 1:1, Rf = 0.20) to
yield 0.57 g (74%) of 70 as a yellow oil with some minor hemiacetal forms present.

$[\alpha]_D^{25} = -25.3$ (c = 0.003 g/mL, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.52 (dd, 1H, $J = 4.8, 8.9$ Hz), 3.88-3.84 (m, 2H), 3.72 (s, 3H), 3.68-3.66 (m, 2H), 3.28 (m, 1H), 3.22-3.19 (t, 1H, $J = 7.0$ Hz), 3.01 (dd, 1H, $J = 10.0, 18.4$ Hz), 2.48 (dd, 1H, $J = 3.7, 18.4$ Hz), 2.24 (m, 1H), 2.12 (s, 3H), 2.02-1.93 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 207.0, 173.6, 173.3, 64.5, 58.8, 52.5, 47.3, 42.1, 41.2, 29.8, 29.0, 24.8. Resonance observed for minor hemiacetal forms: $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.3, 172.6, 172.0, 105.0, 104.9, 69.5, 69.4, 25.1, 24.6. IR (neat, cm$^{-1}$): 3435 (b, OH), 2956-2852, 1743, 1714, 1624, 1447.

(S)-Methyl 1-((S)-2-(((methylthiocarbonothioyloxy)methyl)-4-oxopentanoyl)pyrrolidine-2-carboxylate 72

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with sodium hydride (48 mg, 1.2 mmol, 60% in the mineral oil). Hexanes (2 mL) was added to the flask to wash the sodium hydride. The hexane was removed by syringe, and then tetrahydrofuran (4 mL) was added by syringe. The solution was cooled to 0 °C and carbon disulfide (0.15 g, 2.0 mmol) was added by syringe. After stirring for 5 minutes, compound 70 (0.26 g, 1.0 mmol, in 1 mL of tetrahydrofuran) was added by syringe, followed by methyl iodide (0.21 g, 1.5 mmol). After TLC analysis (hexanes:ethyl acetate = 1:1, $R_f$ = 0.20)
indicated compound 70 was consumed, the solution was quenched with saturated aqueous ammonium chloride (3 mL). The solution was extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 1.5:1, \( R_f = 0.2 \)) to yield 0.24 g (68%) of 72 as a yellow oil. \([\alpha]^{25}_D = -2.0 \) (c = 0.007 g/mL, CHCl₃). \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \): 4.78 (dd, 1H, \( J = 7.3, 10.7 \) Hz), 4.58 (dd, 1H, \( J = 7.3, 10.7 \) Hz), 4.46 (dd, 1H, \( J = 4.6, 8.6 \) Hz), 3.90 (m, 1H), 3.79 (m, 1H), 3.70 (s, 3H), 3.58 (m, 1H), 3.14 (dd, 1H, \( J = 10.4, 18.2 \) Hz), 2.60 (dd, 1H, \( J = 3.3, 18.2 \) Hz), 2.58 (s, 3H), 2.22 (m, 1H), 2.15 (s, 3H), 2.10-1.96 (m, 3H); \(^13\)C NMR (125 MHz, CDCl₃) \( \delta \): 215.5, 206.5, 172.4, 170.5, 72.9, 59.0, 52.2, 47.3, 42.8, 38.1, 29.9, 29.2, 24.9, 19.0. IR (neat, cm\(^{-1}\)): 2955-2850, 1743-1640, 1640, 1214, 1068.

(S)-Methyl 1-((R)-2-methyl-4-oxopentanoyl)pyrrolidine-2-carboxylate 73

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with toluene (4 mL). compound 72 (35 mg, 0.1 mmol), tributyltin hydride (0.05 mL, 0.2 mmol) and AIBN (5 mg, 0.03 mmol) were added to the flask in the indicated order. Then the solution was heated to 80 °C for eight hours. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 3:1, \( R_f = 0.15 \)) to give 17 mg (70%) of 73 as a yellow oil. \(^1\)H NMR (400 MHz, CDCl₃)
8 4.46 (dd, 1H, J = 4.6, 8.7 Hz), 3.83-3.64 (m, 2H), 3.70 (s, 3H), 3.12-2.94 (m, 2H),
2.36 (dd, 1H, J = 3.2, 17.3 Hz), 2.12 (s, 3H), 2.25-1.93 (m, 4H), 1.15 (d, 3H, J = 6.9
Hz), $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.9, 174.5, 172.9, 58.5, 52.1, 47.2, 46.8, 33.1,
30.1, 29.1, 24.9, 16.7. IR (neat, cm$^{-1}$): 2957, 1746, 1645, 1434.

(2S)-Methyl

1-((3S)-5-methyltetrahydrofuran-3-carbonyl)pyrrolidine-2-carboxylate 77A and
77B

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of
nitrogen through a needle and a stir bar, was charged with dichloromethane (6 mL),
compound 76 ((130 mg, 0.5 mmol). After the solution was cooled to the -78 °C,
triethylsilane (0.4 mL, 2.0 mmol) and boron trifluoride diethyl etherate (0.2 mL, 2.0
mmol) were added dropwise in the indicated order. The reaction solution was left
stirring for forty minutes at -78 °C and twenty-one hours at room temperature. The
solution was quenched with saturated sodium bicarbonate solution (5 mL), extracted
with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine
(10 mL) and dried over anhydrous sodium sulfate and concentrated in vacuo. The
product was purified by flash chromatography on silica (hexanes:ethyl acetate = 2:1,
R$_f$ = 0.20) to offer 83 mg (69%) of 77A and 77B as a yellow oily mixture of two
isomers in a 3.3:1 ratio. Major isomer 77A: $^1$H NMR (500 MHz, CDCl$_3$) δ 4.50 (dd,
1H, J = 4.4, 8.7 Hz), 4.22 (dd, 1H, J = 8.4, 8.4 Hz), 4.13-3.97 (m, 2H), 3.72 (s, 3H),

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3.67-3.56 (m, 2H), 3.26 (m, 1H), 2.32 (m, 1H), 2.19 (m, 1H), 2.12-1.82 (m, 3H), 1.63 (m, 1H), 1.26 (d, 3H, J = 6.1 Hz); $^{13}$C (125 MHz, CDCl$_3$) δ 171.7, 171.1, 74.8, 69.2, 57.8, 51.2, 45.9, 42.1, 35.7, 28.0, 23.8, 19.4. Resonances observed for the minor isomer 77B: $^1$H NMR (500 MHz, CDCl$_3$) δ 4.44 (dd, 1H, J = 2.7, 8.6 Hz), 3.77 (s, 3H), 1.30 (d, 3H, J = 6.1 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.5, 171.7, 75.2, 68.5, 58.3, 51.6, 45.8, 43.0, 36.0, 23.5, 19.3.

(2S)-Methyl

1-(2-(2-hydroxypropan-2-yl)-4-oxopentanoyl)pyrrolidine-2-carboxylate 78

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 25 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 10 mL, 10.0 mmol). The solution was cooled to 0 °C and methylene iodide (0.80 mL, 10.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 56 (0.85 g, 4.0 mmol, in 4 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes, at which time freshly distilled acetone (0.4 mL, 4.8 mmol) was added into the reaction mixture by syringe. After TLC analysis (hexanes:ethyl acetate = 3:1, R$_f$ = 0.10) indicated the chain extension intermediate was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (15 mL). The mixture was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with brine (25 mL) and dried over
anhydrous sodium sulfate. The organic solution was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1, $R_f = 0.20$) to yield 0.97 g (80%) of 78 as colorless oil in which one major ring-opened form is present. Major isomer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.46 (dd, 1H, $J = 5.1$, 8.9 Hz), 3.97 (m, 1H), 3.73 (s, 3H), 3.17-2.98 (m, 2H), 2.76 (dd, 1H, $J = 3.0$, 18.3 Hz), 2.39-1.91 (m, 5H), 2.14 (s, 3H), 1.74-1.62 (m, 1H), 1.32 (s, 3H), 1.19 (s, 3H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 208.1, 207.2, 175.3, 174.4, 174.2, 174.1, 173.0, 172.4, 172.3, 172.2, 105.1, 105.0, 84.2, 83.4, 71.4, 70.8, 59.3, 59.1, 58.7, 52.6, 52.4, 52.2, 51.8, 48.4, 47.9, 46.9, 45.8, 42.9, 42.5, 42.2, 42.1, 31.5, 31.4, 30.4, 30.2, 29.5, 29.4, 29.3, 28.8, 27.7, 27.0, 26.4, 26.3, 25.1, 25.0, 24.8; Resonances observed for the another two isomers: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.54 (dd, 1H, $J = 3.1$, 6.1 Hz), 3.75 (s, 3H), 3.72 (s, 3H), 2.21 (s, 3H), 1.52 (s, 6H), 1.41 (s, 3H), 1.35 (s, 3H).

**(2S)-Methyl**

1-(2,2,5-trimethyltetrahydrofuran-3-carbonyl)pyrrolidine-2-carboxylate 80A and 80B

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (8 mL), compound 78 (285 mg, 1.0 mmol). After the solution was cooled to the -78 °C, triethylsilane (0.45 mL, 3.0 mmol) and boron trifluoride diethyl etherate (0.30 mL, 3.0 mmol) were added dropwise in the indicated order. The reaction solution was left

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stirring for forty minutes at -78 °C and twenty-one hours at room temperature. The solution was quenched with saturated sodium bicarbonate solution (5 mL), extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous sodium sulfate and concentrated in vacuo. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 3:1, \( R_f = 0.30 \)) to offer 0.20 g (75\%) of \( 80A \) and \( 80B \) as a yellow oily mixture of two isomers in a 3.5:1 ratio. Major isomer \( 80A \): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.54 (dd, 1H, \( J = 4.6, 8.7 \) Hz), 4.34 (m, 1H), 3.72 (s, 3H), 3.76 (m, 1H), 3.02 (dd, 1H, \( J = 7.4, 8.9 \) Hz), 2.56 (m, 1H), 2.29-1.89 (m, 5H), 1.74-1.62 (m, 1H), 1.47 (s, 3H), 1.24 (d, 3H, \( J = 6.1 \) Hz), 1.21 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 172.9, 171.3, 83.3, 73.2, 59.1, 52.3, 51.7, 47.8, 37.7, 30.4, 29.2, 25.3, 23.6, 22.3. Resonances observed for the minor isomer \( 80B \): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.46 (dd, 1H, \( J = 3.7, 8.1 \) Hz), 3.74 (s, 3H), 3.65 (m, 1H), 2.48 (m, 1H), 1.41 (s, 3H), 1.19 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 173.1, 171.7, 82.5, 73.9, 59.1, 52.4, 52.1, 46.6, 38.2, 30.9, 29.4, 25.1, 24.1, 22.0.

\(((2S)-1-((2,2,5-Trimethyltetrahydrofuran-3-yl)methyl)pyrrolidin-2-yl)methanol\) \( 81 \)

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (10 mL), lithium aluminum hydride (0.15 g, 4.0 mmol) and compound \( 80 \) (0.46 g, 1.7 mmol) in
the indicated order. The solution was refluxed till TLC analysis (hexanes:ethyl acetate = 3:1, \( R_f = 0.30 \)) indicated that the starting material was consumed. The solution was cooled to room temperature and quenched by cautious and sequential addition of water (2 mL), 10% aqueous sodium hydroxide (2 mL), and water (6 mL). After stirring for 10 min, the solution was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 5:1, \( R_f = 0.15 \)) to offer 0.32 g (84%) of 81 as a colorless liquid with a mixture of two isomers in a 3.5:1 ratio. Major isomer: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.04 (m, 1H), 3.50 (dd, 1H, \( J = 5.1, 10.7 \) Hz), 3.36 (dd, 1H, \( J = 2.5, 10.7 \) Hz), 3.14 (m, 1H), 2.88 (b, -OH, 1H), 2.64 (dd, 1H, \( J = 8.4, 12.3 \) Hz), 2.46 (m, 1H), 2.25-1.97 (m, 3H), 1.88-1.58 (m, 6H), 1.26 (s, 3H), 1.22 (d, 3H, \( J = 6.2 \) Hz), 0.97 (s, 3H); \(^{13}\)C (100 MHz, CDCl\(_3\)) \( \delta \) 81.3, 70.0, 64.5, 61.5, 55.0, 53.9, 45.3, 37.6, 27.8, 26.6, 22.7, 22.2, 19.8. Resonances observed for the minor isomer: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.20 (s, 3H), 1.12 (d, 3H, \( J = 6.2 \) Hz), 0.94 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 80.3, 70.6, 64.1, 60.6, 54.3, 52.9, 45.8, 37.2, 27.5, 26.6, 22.4, 22.1, 20.6.

\((2S)-1-((2,2,5\text{-trimethyltetrahydrofuran}-3\text{-yl})\text{methyl})\text{pyrrolidin-2-yl})\text{methyl} 3,5\text{-dinitrobenzoate} 82

A 50-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with pyridine (10 mL), compound 81 (1.0 g, 4.0 mmol), and 3,5-dinitrobenzoylchloride (2.0 g, 8.7 mmol) in
the indicated order. After stirred overnight at room temperature, water (15 mL) was added to the mixture and the solution was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 7:1, R\text{f} = 0.20) to yield 1.35 g (80\%) of 82 as a colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 9.24 (t, 1H, \(J = 2.1\) Hz), 9.16 (d, 2H, \(J = 2.1\) Hz), 4.44 (dd, 1H, \(J = 4.6, 11.0\) Hz), 4.31 (dd, 1H, \(J = 6.3, 11.0\) Hz), 4.10 (m, 1H), 3.22 (m, 1H), 2.86-2.79 (m, 2H), 2.40 (dd, 1H, \(J = 6.0, 12.2\) Hz), 2.24 (m, 1H), 2.14 (m, 1H), 2.00 (m, 1H), 1.88-1.69 (m, 5H), 1.34 (s, 3H), 1.19 (d, 3H, \(J = 6.1\) Hz), 1.05 (s, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 162.7, 148.9, 134.2, 129.6, 122.6, 82.4, 71.3, 69.2, 63.0, 56.9, 54.8, 46.3, 38.8, 29.0, 28.5, 23.6, 23.4, 21.1.

(\textit{S})-Methyl

\textit{1-((\textit{S})-2-(hydroxydiphenylmethyl)-4-oxopentanoyl)pyrrolidine-2-carboxylate} \textit{83}

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 8 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C and methylene iodide (0.20 mL, 2.5 mmol) was added slowly by syringe. After stirring for 10 minutes, compound \textit{55} (0.23 g, 1.0 mmol, in 1 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes, at which time benzophenone (0.29 g 1.6 mmol) was added into
the reaction mixture by syringe. After TLC analysis (hexanes:ethyl acetate = 1.5:1, $R_f = 0.20$) indicated the chain extension intermediate was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (15 mL) and dried over anhydrous sodium sulfate. The organic solution was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1, $R_f = 0.30$) to yield 0.26 g (65%) of 83 as colorless oil in which one major ring-opening form is present.

(5)-Methyl 1-((2S,4S)-4-hydroxy-2-(hydroxydiphenylmethyl)pentanoyl)pyrrolidine-2-carboxylate 85

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (8 mL), compound 83 (286 mg, 0.7 mmol). After the solution was cooled to the -78 °C, triethylsilane (0.39 mL, 2.4 mmol) and boron trifluoride diethyl etherate (0.30 mL, 3.0 mmol) were added dropwise in the indicated order. The reaction solution was left stirring for forty minutes at -78 °C and twenty-one hours at room temperature. The solution was quenched with saturated sodium bicarbonate solution (5 mL), extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous sodium sulfate and concentrated in vacuo. The
product was purified by flash chromatography on silica (hexanes:ethyl acetate = 4:1, \( R_f = 0.20 \)) to offer 0.20 g (70%) of 85 as a yellow oily mixture of two rotamers in a 3:1 ratio. Major rotamer: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.59-7.14 (m, 10H), 4.05 (dd, 1H, \( J = 2.2, 8.4 \) Hz), 3.98 (m, 1H), 3.79 (s, 3H), 3.76 (dd, 1H, \( J = 1.8, 8.5 \) Hz), 3.40 (m, 1H), 2.85 (m, 1H), 2.24 (m, 1H), 2.00 (m, 1H), 1.81 (m, 1H), 1.65-1.52 (m, 2H), 1.59 (d, 3H, \( J = 6.1 \) Hz), 1.40-1.20 (m, 2H), 0.86 (m, 1H); \(^{13}\)C (100 MHz, CDCl\(_3\)) \( \delta \): 173.0, 171.3, 143.5, 141.9, 128.5, 127.6, 127.4, 126.8, 126.2, 90.9, 72.8, 59.1, 52.7, 51.1, 46.0, 35.5, 30.5, 22.0, 20.2. Resonances observed for the minor rotamer: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 4.28 (dd, 1H, \( J = 4.9, 8.6 \) Hz), 4.10 (m, 1H), 3.57 (s, 3H), 1.52 (d, 3H, \( J = 6.0 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 172.5, 171.2, 146.2, 142.5, 128.4, 127.6, 127.1, 90.0, 73.1, 53.4, 52.1, 47.5, 37.6, 28.8, 25.1, 20.4.

\((S)\)-Methyl 2-(N-benzyl-3-oxobutanamido)-3-phenylpropanoate 94

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with (S)-methyl 2-(benzylamino)-3-methylbutanoate (2.50 g, 9.3 mmol), benzene (40 mL), sodium bicarbonate (1.7 g, 20 mmol) and diketene (1.5 mL, 19 mmol) in the indicated order. The suspension was stirred overnight at room temperature. The resulting liquid was filtered through filter paper and ethyl acetate (40 mL) was added to the filtrate. The organic solution was washed with 1 M HCl (20 mL), brine (20 mL), saturated sodium bicarbonate solution (20 mL), and brine (20 mL). The solution was concentrated
under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 5:1, \( R_f = 0.20 \)) to offer 2.0 g (61\%) of 94 as a yellow oily mixture of two rotamers with some minor enol forms present. (NMR spectrum available in the CD)

\[(S)\]-Methyl 2-(N-benzyl-4-oxopentanamido)-3-phenylpropanoate 95

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 40 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 15 mL, 15.0 mmol). The solution was cooled to 0 °C and methylene iodide (1.2 mL, 15.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 93 (1.06 g, 3.0 mmol, in 3 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. After TLC analysis (hexanes:ethyl acetate = 3:1; \( R_f = 0.20 \)) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (25 mL). The mixture was extracted with diethyl ether (2 x 30 mL), washed with brine (25 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1; \( R_f = 0.15 \)) to yield 0.80 g (73\%) of 95 as a yellow oily compound. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.29-7.07 (m, 10H), 4.46 (d, 1H, \( J = 16.8 \) Hz), 4.22 (dd, 1H, \( J = 5.8, 9.2 \) Hz), 3.81 (d, 1H, \( J = 16.9 \) Hz), 3.59 (s, 3H), 3.30 (dd,
$^{1}H, J = 3.2, 13.9\text{ Hz}$, 3.16 (dd, $1^H, J = 9.2, 13.9\text{ Hz}$), 2.84 (m, $1^H$), 2.71-2.58 (m, 2H), 2.45 (m, $1^H$), 2.18 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl$_3$) $\delta$ 207.5, 172.5, 171.0, 138.3, 136.3, 129.6, 128.8, 127.8, 127.5, 126.8, 61.8, 52.6, 52.2, 38.2, 35.4, 30.2, 27.7.

**(S)-Methyl 2-(N-benzyl-4-oxopentanamido)-3-methylbutanoate 96**

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 30 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 15 mL, 15.0 mmol). The solution was cooled to 0 °C and methylene iodide (1.2 mL, 15.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 94 (0.92 g, 3.0 mmol, in 3 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. After TLC analysis (hexanes:ethyl acetate = 3:1; $R_f = 0.20$) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (25 mL). The mixture was extracted with diethyl ether (3 x 30 mL), washed with brine (25 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 1.5:1, $R_f = 0.15$) to yield 0.69 g (72%) of 96 as a yellow oily mixture of two rotamers in a 2.2:1 ratio. Major rotamer: $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.26-7.03 (m, 5H), 4.74 (d, $1^H, J = 10.4\text{ Hz}$), 4.61-4.53 (m, 2H), 3.29 (s, 3H), 2.84 (m, 1H), 2.71-2.58 (m, 2H), 2.45 (m, $1^H$), 2.18 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl$_3$) $\delta$ 207.5, 172.5, 171.0, 138.3, 136.3, 129.6, 128.8, 127.8, 127.5, 126.8, 61.8, 52.6, 52.2, 38.2, 35.4, 30.2, 27.7.
2.77-2.66 (m, 2H), 2.53 (m, 1H), 2.30-2.15 (m, 2H), 2.04 (s, 3H), 0.84 (d, 3H, J = 6.6
Hz), 0.76 (d, 3H, J = 6.8 Hz); $^1$C (100 MHz, CDCl$_3$) $\delta$ 207.4, 173.4, 171.0, 137.2,
observed for the minor rotamer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.20 (s, 3H), 2.10 (s,
3H); $^1$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.8, 170.2, 137.8, 128.2, 127.6, 126.8, 51.8,
45.8, 38.3, 30.2, 27.5.

$(S)$-Methyl 2-(4-oxopentanamido)-3-phenylpropanoate 97

A 50-mL round-bottomed flask was equipped with a stir bar and charged with
acetonitrile (16 mL), water (4 mL), and the $\gamma$-keto amide compound 100 (0.50 g, 1.25
mmol). To this solution was added ceric ammonium nitrate (2.6 g, 5.0 mmol) and the
mixture was allowed to stir for half hour under room temperature. The solution was
added water (10 mL), then extracted with Et$_2$O (3 x 15 mL). The combined organic
extracts were dried carefully over anhydrous sodium sulfate and concentrated in
vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 1.5:1, $R_f$ =
0.20) yielded 0.20 g (58%) of 97 as a viscous colorless oil. $^1$H NMR (400 MHz,
CDCl$_3$) $\delta$ 7.31-7.11 (m, 5H), 6.20 (d, 1H, J = 7.7 Hz), 4.84 (dd, 1H, J = 5.9, 13.7 Hz),
3.71 (s, 3H), 3.14 (dd, 1H, J = 5.8, 13.9 Hz), 3.06 (dd, 1H, J = 6.0, 13.9 Hz),
2.82-2.68 (m, 2H), 2.50-2.37 (m, 2H), 2.16 (s, 3H); $^1$C NMR (100 MHz, CDCl$_3$) $\delta$
207.6, 172.2, 171.7, 136.1, 129.5, 128.8, 127.3, 53.4, 52.5, 38.5, 38.1, 30.1, 29.9.
(S)-Methyl 2-(N-(4-methoxybenzyl)-3-oxobutanamido)-3-phenylpropanoate 98

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with (S)-methyl 2-(4-methoxybenzylamino)-3-phenylpropanoate (4.3 g, 16 mmol), benzene (40 mL), sodium bicarbonate (2.4 g, 30 mmol) and diketene (3.4 mL, 40 mmol) in the indicated order. The suspension was stirred overnight at room temperature. The resulting liquid was filtered through filter paper and ethyl acetate (100 mL) was added to the filtrate. The organic solution was washed with 1 M HCl (50 mL), brine (50 mL), saturated sodium bicarbonate solution (50 mL), and brine (50 mL). The solution was concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 3:1, Rf = 0.25) to offer 4.5 g (73%) of 98 as a yellow oily mixture of two rotamers, with some minor enol forms present.

Major rotamer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31-6.78 (m, 9H), 4.50-4.28 (m, 3H), 3.78 (s, 3H), 3.66 (s, 3H), 3.49 (s, 2H), 3.38 (m, 1H), 3.23 (m, 1H), 2.23 (s, 3H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 202.1, 176.2, 172.9, 171.3, 170.6, 167.6, 159.5, 159.2, 138.0, 129.8, 129.6, 129.5, 129.0, 128.8, 128.6, 127.5, 127.0, 126.8, 114.3, 114.1, 113.9, 61.2, 60.8, 55.5, 52.6, 52.4, 51.5, 50.5, 35.8, 35.4, 30.4, 22.3. Resonances observed for the enol forms: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.06 (s, 1H), 3.66 (s, 3H), 1.92 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 87.8.
(S)-Methyl 2-(N-(4-methoxybenzyl)-3-oxobutanamido)-3-methylbutanoate 99

A 250-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with (S)-methyl 2-(4-methoxybenzylamino)-3-methylbutanoate (5.0 g, 20 mmol), benzene (80 mL), sodium bicarbonate (3.4 g, 40 mmol) and diketene (4.2 mL, 50 mmol) in the indicated order. The suspension was stirred overnight at room temperature. The resulting liquid was filtered through filter paper and ethyl acetate (100 mL) was added to the filtrate. The organic solution was washed with 1 M HCl (50 mL), brine (50 mL), saturated sodium bicarbonate solution (50 mL), and brine (50 mL). The solution was concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 5:1, Rf = 0.25) to offer 4.0 g (60%) 99 as a yellow oily mixture two rotamers with some minor enol forms present. Major rotamer: 1H NMR (400 MHz, CDCl3) δ 7.21-6.79 (m, 4H), 4.86 (m, 1H), 4.57-4.50 (m, 2H), 3.80 (s, 3H), 3.48 (s, 3H), 3.41 (d, 2H, J = 10.9 Hz), 2.21 (s, 3H), 2.37-2.28 (m, 1H), 0.98 (d, 3H, J = 6.4 Hz), 0.94 (d, 3H, J = 6.8 Hz); 13C (100 MHz, CDCl3) δ 202.4, 176.2, 173.4, 168.5, 159.2, 129.8, 128.6, 127.7, 127.4, 114.4, 114.1, 113.7, 66.6, 62.3, 61.2, 55.5, 55.4, 52.2, 51.9, 51.1, 50.5, 48.6, 47.7, 45.8, 30.7, 30.2, 28.2, 27.9, 27.7, 22.3, 20.2, 20.1, 19.0, 18.9. Resonances observed for the minor rotamer: 1H NMR (400 MHz, CDCl3) δ 3.77 (s, 3H), 3.49 (s, 3H), 2.31 (s, 3H), 0.86 (d, 3H, J = 6.7 Hz), 0.80 (d, 3H, J = 6.7 Hz). Resonances observed for the enol forms: 1H NMR (400 MHz, CDCl3) δ 5.06 (s, 1H), 1.89 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 87.9.
(S)-Methyl 2-(N-(4-methoxybenzyl)-4-oxopentanamido)-3-phenylpropanoate 100

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 40 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 15 mL, 15.0 mmol). The solution was cooled to 0 °C and methylene iodide (1.2 mL, 15.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 98 (1.15 g, 3.0 mmol, in 3 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. After TLC analysis (hexanes:ethyl acetate = 3:1, Rf = 0.25) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (25 mL). The mixture was extracted with diethyl ether (2 x 30 mL), washed with brine (25 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1; Rf = 0.20) to yield 0.77 g (65%) of 100 as a yellow oily mixture of two rotamers in a 7:1 ratio. Major rotamer: 1H NMR (500 MHz, CDCl3) δ 7.30-7.21 (m, 3H), 7.13 (d, 2H, J = 7.5 Hz), 7.09 (d, 2H, J = 8.4 Hz), 6.81 (d, 2H, J = 8.5 Hz), 4.42 (d, 1H, J = 16.5 Hz), 4.18 (dd, 1H, J = 5.6, 9.2 Hz), 3.77 (s, 3H), 3.74 (d, 1H, J = 16.4 Hz), 3.62 (s, 3H), 3.32 (dd, 1H, J = 5.7, 14.0 Hz), 3.18 (dd, 1H, J = 9.4, 13.8 Hz), 2.86 (m, 1H), 2.74-2.62 (m, 2H), 2.50 (m, 1H), 2.21 (s, 3H); 13C (100 MHz, CDCl3) δ 207.5, 172.3, 171.0, 159.3, 138.4, 129.6, 128.9, 128.7, 126.8, 114.1, 61.5, 55.4, 52.2, 38.1, 35.4, 30.2, 27.7, 21.2. Resonances observed for the minor rotamer:
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 4.68 (m, 1H), 3.38 (s, 3H), 3.04 (dd, 1H, $J = 8.3$, 14.1 Hz), 2.17 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.7, 171.2, 137.0, 129.4, 127.1, 113.8, 60.5, 46.2, 38.5, 36.0, 27.5.

((S)-Methyl 2-(N-(4-methoxybenzyl)-4-oxopentanamido)-3-methylbutanoate 101

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 40 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 15 mL, 15.0 mmol). The solution was cooled to 0 °C and methylene iodide (1.2 mL, 15.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 99 (1.0 g, 3.0 mmol, in 3 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. After TLC analysis (hexanes:ethyl acetate = 5:1, $R_f = 0.25$) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (25 mL). The mixture was extracted with diethyl ether (3 x 20 mL), washed with brine (25 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 5:1, $R_f = 0.20$) to yield 1.04 g (84%) of 101 as a yellow oily mixture of two rotamers in a 2.5:1 ratio. Major rotamer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.05 (d, 2H, $J = 8.5$ Hz), 6.77 (d, 2H, $J = 8.5$ Hz), 4.68 (d, 1H, $J = 10.3$ Hz), 4.56 (d, 1H, $J = 17.3$ Hz), 4.59 (d, 1H, $J = 17.2$ Hz), 3.67 (s, 3H), 3.35 (s, 3H), 2.84-2.53 (m, 162
3H), 2.37-2.20 (m, 2H), 2.07 (s, 3H), 0.86 (d, 3H, J = 6.5 Hz), 0.76 (d, 3H, J = 5.8 Hz); $^{13}$C (125 MHz, CDCl$_3$) δ 207.5, 173.3, 171.0, 158.9, 129.1, 127.5, 114.1, 77.8, 62.4, 55.4, 51.7, 48.3, 38.3, 30.1, 27.9, 20.1, 18.8. Resonances observed for the minor rotamer: $^1$H NMR (500 MHz, CDCl$_3$) δ 7.02 (d, 2H, J = 8.6 Hz), 6.68 (d, 2H, J = 8.6 Hz), 4.75 (d, 1H, J = 15.2 Hz), 4.10 (d, 1H, J = 14.3 Hz), 3.97 (d, 1H, J = 10.9 Hz), 3.64 (s, 3H), 3.28 (s, 3H), 2.12 (s, 3H), 0.88 (d, 3H, J = 6.6 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.5, 172.6, 170.3, 158.6, 130.0, 128.9, 113.5, 77.7, 65.6, 62.3, 55.3, 51.9, 51.6, 45.3, 27.5.

**{(S)-Methyl 3-methyl-2-(4-oxopentanamido)butanoate 102}**

A 50-mL round-bottomed flask was equipped with a stir bar and charged with acetonitrile (16 mL), water (4.0 mL), and compound 101 (0.54 g, 1.5 mmol). To this solution was added ceric ammonium nitrate (3.1 g, 6.0 mmol) and the mixture was allowed to stir for half hour at room temperature. The solution was added water (10 mL), then extracted with Et$_2$O (3 x 15 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 1:1, R$_f$ = 0.25) yielded 0.21 g (60%) of 102 as a viscous colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 6.35 (d, 1H, J = 8.4 Hz), 4.44 (dd, 1H, J = 6.1, 8.8 Hz), 3.66 (s, 3H), 2.82-2.65 (m, 2H), 2.51-2.40 (m, 2H), 2.12 (s, 3H), 2.08 (m, 1H), 0.86 (d, 3H, J = 6.9 Hz), 0.84 (d, 3H, J = 6.9 Hz);
(S)-Methyl 2-(2-(hydroxymethyl)-N-(4-methoxybenzyl)-4-oxopentanamido)-3-phenylpropanoate 103A and 103B

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 8 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C and methylene iodide (0.20 mL, 2.5 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 98 (0.38 g, 1.0 mmol, in 1 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. Paraformaldehyde (0.3 g) was placed in a dry one-necked round-bottomed flask, which was capped with a rubber septum. One end of a cannula was inserted through the septum in the flask that contained paraformaldehyde, and the other end of the cannula was inserted through the septum in the flask that contained the zinc reagent. The paraformaldehyde flask was heated with a heat gun to induce formation of formaldehyde, which was bubbled into the zinc-carbenoid solution for 10 minutes. After TLC analysis (hexanes:ethyl acetate = 3:1, Rf = 0.25) indicated the chain extension intermediate was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The solution was extracted

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3 \delta 207.8, 172.7, 172.1, 57.3, 52.2, 38.6, 31.3, 30.0, 29.9, 19.1, 18.0. } \]
with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (15 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 2:1, Rf = 0.20) to yield 0.33 g (78%) of 103A and 103B as a yellow oily mixture of two isomers with some minor hemiacetal forms present. ¹H NMR (500 MHz, CDCl₃) δ 7.31-6.96 (m, 7H), 6.83-6.79 (m, 2H), 4.56 (m, 1H), 4.38-3.85 (m, 2H), 3.78-3.60 (m, 8H), 3.4-2.98 (m, 4H), 2.70 (m, 1H), 2.19-2.03 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 207.0, 175.5, 171.3, 170.5, 159.5, 138.5, 129.7, 129.4, 128.9, 128.4, 114.4, 69.9, 64.0, 63.3, 62.0, 61.6, 60.7, 55.5, 52.9, 52.1, 42.9, 41.2, 39.2, 35.8, 35.4, 30.2, 25.3. Resonance observed for hemiacetal: ¹³C NMR (125 MHz, CDCl₃) δ 105.3.

(5)-Methyl 2-(2-((tert-butyldimethylsilyloxy)methyl)-N-(4-methoxybenzyl)-4-oxopentanamido)-3-phenylpropanoate 105A and 105B

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with N,N-dimethylformamide (4 mL), compound 103 (0.21 g, 0.5 mmol), tert-butylchlorodimethylsilane (0.12g, 0.75 mmol) and imidazole (90 mg, 1.25 mmol) in the indicated order. After being stirred overnight at room temperature, water (2 mL) was added to the mixture and the solution was extracted with diethyl ether (3 x 5 mL). The combined organic extracts
were dried carefully over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica (hexanes:ethyl acetate = 10:1, \( R_f = 0.25 \)) to yield 0.89 g (60\%) of **105A** (32\%) and **105B** (28\%) as a colorless oil. **105A** : \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.30-7.38 (m, 4H), 7.24 (m, 1H), 7.12 (d, 2H, \( J = 8.4 \) Hz), 6.89 (d, 2H, \( J = 8.7 \) Hz), 4.62 (d, 1H, \( J = 16.3 \) Hz), 4.25 (d, 1H, \( J = 16.2 \) Hz), 4.21 (dd, 1H, \( J = 6.3, 7.8 \) Hz), 3.84 (s, 3H), 3.66 (dd, 1H, \( J = 5.3, 9.5 \) Hz), 3.63 (s, 3H), 3.48-3.38 (m, 3H), 3.08 (dd, 1H, \( J = 9.2, 16.4 \) Hz), 3.04 (dd, 1H, \( J = 3.0, 15.1 \) Hz), 3.04 (dd, 1H, \( J = 3.0, 11.1 \) Hz), 2.79 (dd, 1H, \( J = 3.8, 18.2 \) Hz), 2.24 (s, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 213.1, 179.1, 176.4, 164.8, 144.1, 135.1, 134.8, 134.0, 133.9, 132.0, 119.6, 69.3, 67.0, 60.9, 57.6, 49.1, 46.4, 41.4, 35.7, 31.5, 23.8, 0.10, 0.00. **105B** : \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.29-7.22 (m, 5H), 7.11 (d, 2H, \( J = 8.2 \) Hz), 6.84 (d, 2H, \( J = 8.7 \) Hz), 4.44 (d, 1H, \( J = 16.0 \) Hz), 4.08 (dd, 1H, \( J = 5.9, 8.8 \) Hz), 3.79 (m, 1H), 3.79 (s, 3H), 3.72 (dd, 1H, \( J = 5.8, 9.6 \) Hz), 3.55 (m, 1H), 3.54 (s, 3H), 3.42 (m, 1H), 3.36 (dd, 1H, \( J = 6.0, 14.1 \) Hz), 3.10 (dd, 1H, \( J = 8.9, 14.0 \) Hz), 2.92 (dd, 1H, \( J = 8.8, 17.8 \) Hz), 2.63 (dd, 1H, \( J = 4.4, 17.9 \) Hz), 2.14 (s, 3H), 0.88 (s, 9H), 0.88 (s, 3H), 0.07 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 212.6, 178.6, 176.2, 164.7, 143.9, 135.0, 134.9, 133.9, 132.1, 119.3, 69.5, 66.0, 60.7, 57.3, 48.5, 46.2, 40.8, 35.7, 31.4, 23.8, 6.5, 0.0.
(S)-Methyl
2-((S)-2-((tert-butyldiphenylsilyloxy)methyl)-N-(4-methoxybenzyl)-4-oxopentanamido)-3-phenylpropanoate 107A and 107B

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with N,N-dimethylformamide (10 mL), compound 103 (0.80 g, 2.0 mmol), tert-butylchlorodiphenylsilane (1.4 mL, 5.0 mmol) and imidazole (0.14 mg, 4.0 mmol) in the indicated order. After being stirred overnight at room temperature, water (6 mL) was added to the mixture and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 7:1, Rf = 0.40) to yield 0.77 g (58%) of 107A and 107B as a colorless oil. 107B: ¹H NMR (500 MHz, CDCl₃) δ 7.65-7.63 (d, 2H, J = 7.9 Hz), 7.58-7.57 (d, 2H, J = 8.0 Hz), 7.44-7.38 (m, 3H), 7.31 (m, 1H), 7.28-7.24 (m, 2H), 7.13-7.09 (m, 3H), 7.04 (d, 1H, J = 7.6 Hz), 7.03 (d, 1H, J = 7.3 Hz), 6.94 (d, 2H, J = 8.3 Hz), 6.80 (d, 2H, J = 8.7 Hz), 4.16 (d, 1H, J = 15.9 Hz), 3.84 (dd, 1H, J = 5.6, 9.5 Hz), 3.78 (s, 3H), 3.70 (dd, 1H, J = 5.6, 9.1 Hz), 3.64 (dd, 1H, J = 5.6, 10.1 Hz), 3.50 (s, 3H), 3.42 (m, 1H), 3.26 (dd, 1H, J = 3.6, 13.9 Hz), 3.19 (d, 1H, J = 15.8 Hz), 3.05 (d, 1H, J = 9.4 Hz), 3.02 (dd, 1H, J = 3.3, 9.4 Hz), 2.78 (dd, 1H, J = 3.8, 17.8 Hz), 2.16 (s, 3H), 1.04 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 207.4, 172.2, 170.6, 159.2, 138.2, 135.6, 133.0, 130.0, 129.8, 129.3,
(S)-Methyl

2-(2-((tert-butyldiphenylsilyloxy)methyl)-4-oxopentanamido)-3-phenylpropanoate 108A

A 10-mL round-bottomed flask was equipped with a stir bar and charged with acetonitrile (2 mL), water (0.5 mL), and 107A (66 mg, 0.1 mmol). To this solution was added ceric ammonium nitrate (0.22 g, 0.4 mmol) and the mixture was allowed to stir for 30 min at room temperature. The solution was added water (1.5 mL), then extracted with Et₂O (3 x 5 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1, R_f = 0.20) and yielded 33 mg (60%) of 108A as a viscous colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.62-7.60 (m, 4H), 7.47-7.35 (m, 6H), 7.29-7.21 (m, 3H), 7.14 (d, 2H, J = 8.4 Hz), 6.74 (d, 1H, J = 7.8 Hz), 4.87 (dd, 1H, J = 6.2, 14.1 Hz), 3.80 (dd, 1H, J = 7.8, 10.1 Hz), 3.64 (s, 3H), 3.60 (dd, 1H, J = 5.7, 10.2 Hz), 3.13 (dd, 1H, J = 5.9, 13.8 Hz), 3.04 (dd, 1H, J = 6.3, 13.8 Hz), 2.94 (m, 1H), 2.80 (dd, 1H, J = 8.5, 18.1 Hz), 2.44 (dd, 1H, J = 4.6, 18.2 Hz), 2.08 (s, 3H), 1.00 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 207.4, 172.6, 171.7, 135.6, 129.4, 128.5, 127.8, 64.4, 53.4, 52.1, 43.7, 41.7, 38.2, 30.1, 26.8, 19.1.
(S)-Methyl

2-(2-((tert-butylphenylsilyloxy)methyl)-4-oxopentanamido)-3-phenylpropanoate 108B

A 10-mL round-bottomed flask was equipped with a stir bar and charged with acetonitrile (2 mL), water (0.5 mL), and compound 107B (66 mg, 0.1 mmol). To this solution was added ceric ammonium nitrate (0.22 g, 0.4 mmol) and the mixture was allowed to stir for 30 min at room temperature. The solution was added water (1.5 mL), then extracted with Et₂O (3 x 5 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1, Rf = 0.25) and yielded 36 mg (65%) of 108B as a viscous colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.64-7.60 (m, 4H), 7.47-7.43 (m, 2H), 7.41-7.37 (m, 4H), 7.18-7.17 (m, 3H), 7.08-7.05 (m, 2H), 6.76 (d, 1H, J = 7.9 Hz), 4.84 (dd, 1H, J = 6.4, 14.3 Hz), 3.76 (dd, 1H, J = 7.5, 10.3 Hz), 3.68 (s, 3H), 3.61 (dd, 1H, J = 6.0, 10.2 Hz), 3.09 (dd, 1H, J = 6.1, 13.8 Hz), 3.02 (dd, 1H, J = 6.6, 13.8 Hz), 2.96 (m, 1H), 2.76 (dd, 1H, J = 8.0, 18.0 Hz), 2.50 (dd, 1H, J = 5.0, 18.0 Hz), 2.09 (s, 3H), 1.03 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 206.8, 172.6, 171.8, 136.1, 135.6, 129.9, 129.2, 128.5, 127.8, 127.0, 64.3, 53.3, 52.2, 43.7, 41.8, 38.2, 30.1, 26.8, 19.2..
(S)-Methyl

2-(N-(4-methoxybenzyl)-2-((methylthiocarbonothioyloxy)methyl)-4-oxopentanamido)-3-phenylpropanoate 110A and 110B

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with sodium hydride (40 mg, 1.0 mmol, 60 % in the mineral oil). Hexanes (2 mL) was added to the flask to wash the sodium hydride. The hexane was removed by syringe, and then tetrahydrofuran (4 mL) was added by syringe. The solution was cooled to 0 °C and carbon disulfide (0.06 g, 1.0 mmol) was added by syringe. After stirring for 5 minutes, compound 103 (0.21 g, 0.5 mmol, in 1 mL of tetrahydrofuran) was added by syringe, followed by methyl iodide (0.14 g, 1.0 mmol). After TLC analysis (hexanes:ethyl acetate = 2:1, Rf = 0.20) indicated that 103 was consumed, the solution was quenched with saturated aqueous ammonium chloride (3 mL). The solution was extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1, Rf = 0.20) to yield 0.18 g (62%) of 110A (35%) and 110B (27%) as a yellow oily mixture. 110A: two rotamers in a 5:1 ratio. Major rotamer: 1H NMR (500 MHz, CDCl3) δ 7.32-7.24 (m, 3H), 7.20 (d, 2H, J = 8.7 Hz), 7.11 (d, 2H, J = 8.3 Hz), 6.83 (d, 2H, J = 8.7 Hz), 4.70 (dd, 1H, J = 6.6, 10.7 Hz), 4.62 (d, 1H, J = 16.0 Hz), 4.42 (dd, 1H, J = 7.4, 10.8 Hz), 4.18 (d, 1H, J = 16.0 Hz), 4.06 (dd, 1H, J = 6.0, 8.0 Hz),
3.79 (s, 3H), 3.76 (m, 1H), 3.61 (s, 3H), 3.44 (dd, 1H, J = 5.9, 14.1 Hz), 3.17 (dd, 1H, J = 9.3, 18.2 Hz), 3.02 (dd, 1H, J = 8.0, 14.1 Hz), 2.66 (dd, 1H, J = 4.2, 18.2 Hz), 2.55 (s, 3H), 2.22 (s, 3H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 215.7, 206.2, 172.2, 170.9, 159.5, 138.7, 129.8, 129.7, 128.6, 127.8, 126.7, 114.3, 73.3, 61.7, 55.5, 52.7, 52.3, 43.5, 37.0, 35.7, 30.2, 19.5. Resonances observed for the minor rotamer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.97 (m, 1H), 3.77 (s, 3H), 3.48 (s, 3H), 2.04 (s, 3H). 110B: mixture of two rotamers in a 7:1 ratio. Major rotamer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26-7.20 (m, 5H), 7.05 (d, 2H, J = 8.3 Hz), 6.84 (d, 2H, J = 8.7 Hz), 4.75 (dd, 1H, J = 6.4, 10.7 Hz), 4.61 (d, 1H, J = 15.9 Hz), 4.50 (dd, 1H, J = 7.0, 10.7 Hz), 4.03 (dd, 1H, J = 5.3, 9.6 Hz), 3.78 (s, 3H), 3.74 (m, 1H), 3.66 (d, 1H, J = 15.9 Hz), 3.59 (s, 3H), 3.36 (dd, 1H, J = 5.3, 14.0 Hz), 3.19 (dd, 1H, J = 9.7, 13.9 Hz), 3.04 (dd, 1H, J = 8.5, 17.9 Hz), 2.58 (s, 3H), 2.57 (m, 1H), 2.14 (s, 3H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 215.8, 206.0, 171.8, 170.7, 159.5, 138.4, 129.9, 129.6, 128.9, 127.5, 126.9, 114.1, 73.3, 61.3, 55.5, 52.1, 52.3, 43.0, 37.1, 35.7, 30.2, 19.6. Resonances observed for the minor rotamer: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.98 (m, 1H), 3.77 (s, 3H), 3.36 (s, 3H), 2.54 (s, 3H), 2.11 (s, 3H).

(S)-Methyl

2-(N-(4-methoxybenzyl)-2-methyl-4-oxopentanamido)-3-phenylpropanoate 111A

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with toluene (4 mL). Compound
110A (88 mg, 0.17 mmol), tributyltinhydride (0.10 mL, 0.4 mmol) and AIBN (10 mg, 0.06 mmol) were added sequentially to the flask. The solution was heated to 80 °C for 8 h. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 3:1, Rf = 0.25) to give 50 mg (71%) of 111A. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.27-7.18 (m, 5H), 7.10 (d, 2H, J = 8.3 Hz), 6.83 (d, 2H, J = 8.7 Hz), 4.52 (d, 1H, J = 16.1 Hz), 4.09 (dd, 1H, J = 5.7, 18.3 Hz), 4.04 (d, 1H, J = 16.1 Hz), 3.79 (s, 3H), 3.62 (s, 3H), 3.42 (dd, 1H, J = 5.7, 14.1 Hz), 3.20-3.13 (m, 2H), 3.06 (dd, 1H, J = 8.4, 14.1 Hz), 2.42 (d, 1H, J = 4.0 Hz), 2.18 (s, 3H), 1.01 (d, 3H, J = 6.7 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.5, 176.0, 170.9, 159.2, 138.6, 129.5, 129.2, 128.9, 128.1, 126.4, 114.0, 61.2, 55.3, 52.0, 47.7, 35.6, 31.8, 30.1, 17.2.

(iS)-Methyl 2-(N-(4-methoxybenzyl)-2-((methylthiocarbonothioyloxy)(phenyl)methyl)-4-oxopentanamido)-3-phenylpropanoate 113A and 113B

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with sodium hydride (40 mg, 1.0 mmol, 60 % in the mineral oil). Hexanes (2 mL) was added to the flask to wash the sodium hydride. The hexane was removed by syringe, and then tetrahydrofuran (4 mL) was added by syringe. The solution was cooled to 0 °C and carbon disulfide (0.06 g, 1.0 mmol) was added by syringe. After stirring for 5 minutes, compound 112 (0.25 g,
0.5 mmol, in 1 mL of tetrahydrofuran) was added by syringe, followed by methyl iodide (0.14 g, 1.0 mmol). After TLC analysis (hexanes:ethyl acetate = 1:1, Rf = 0.30) indicated 112 was consumed, the solution was quenched with saturated aqueous ammonium chloride (3 mL). The solution was extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1, Rf = 0.20) to yield 0.12 g (40%) of 113A (20%) and 113B (20%) as a yellow oily mixture. 113A: \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.35-7.18 (m, 5H), 7.14-7.12 (m, 2H), 7.07-7.05 (m, 2H), 6.88 (d, 2H, \( J = 8.7 \) Hz), 6.78-6.74 (m, 3H), 4.52 (d, 1H, \( J = 16.1 \) Hz), 3.91-3.83 (m, 3H), 3.78 (s, 3H), 3.54 (s, 3H), 3.40 (dd, 1H, \( J = 6.0, 14.1 \) Hz), 3.15-3.10 (m, 2H), 2.92 (dd, 1H, \( J = 7.8, 14.1 \) Hz), 2.79 (dd, 1H, \( J = 4.8, 17.9 \) Hz), 2.55 (s, 3H), 2.21 (s, 3H); \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 214.2, 206.4, 171.6, 170.8, 159.5, 138.7, 137.5, 129.7, 129.6, 128.7, 128.6, 127.4, 126.7, 114.2, 84.2, 61.5, 58.5, 52.4, 52.2, 43.7, 43.2, 35.3, 30.5, 19.2.

113B: \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.39-7.34 (m, 4H), 7.13-7.11 (m, 3H), 6.82-6.77 (m, 4H), 6.74-6.67 (m, 3H), 4.45 (d, 1H, \( J = 15.5 \) Hz), 4.06 (m, 1H), 3.98 (d, 1H, \( J = 15.6 \) Hz), 3.84 (dd, 1H, \( J = 6.5, 6.5 \) Hz), 3.77 (s, 3H), 3.76 (m, 1H), 3.56 (s, 3H), 3.36 (dd, 1H, \( J = 6.2, 14.1 \) Hz), 2.92 (dd, 1H, \( J = 6.5, 17.8 \) Hz), 2.79 (dd, 1H, \( J = 5.4, 17.8 \) Hz), 2.65 (dd, 1H, \( J = 7.4, 14.1 \) Hz), 2.53 (s, 3H), 2.17 (s, 3H); \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 214.4, 206.0, 171.8, 170.8, 159.5, 138.7, 137.8, 129.8, 129.5, 128.9, 128.8,
(S)-Methyl

2-(2-benzyl-N-(4-methoxybenzyl)-4-oxopentanamido)-3-phenylpropanoate 114A

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with toluene (4 mL). Compound 113A (59 mg, 0.1 mmol), tributyltinhydride (0.05 mL, 0.2 mmol) and AIBN (5 mg, 0.03 mmol) were added to the flask in the indicated order. Then the solution was heated to 80 °C for 8 hours. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 5:1, Rf = 0.10) to give 26 mg (54 %) of 114A as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.28-7.11 (m, 10H), 6.92 (d, 2H, $J$ = 8.1 Hz), 6.82 (d, 2H, $J$ = 8.7 Hz), 4.63 (d, 1H, $J$ = 16.4 Hz), 4.12 (dd, 1H, $J$ = 5.9, 8.2 Hz), 4.02 (d, 1H, $J$ = 16.4 Hz), 3.78 (s, 3H), 3.66 (s, 3H), 3.45 (dd, 1H, $J$ = 5.8, 14.2 Hz), 3.32 (m, 1H), 3.06-3.01 (m, 2H), 2.86 (dd, 1H, $J$ = 5.1, 13.6 Hz), 2.48 (dd, 1H, $J$ = 9.6, 13.7 Hz), 2.38 (dd, 1H, $J$ = 4.0, 18.1 Hz), 2.12 (s, 3H); $^{13}$C (125 MHz, CDCl$_3$) δ 207.6, 175.5, 171.1, 159.4, 138.9, 138.8, 138.1, 129.7, 129.3, 129.2, 128.7, 128.6, 126.7, 114.3, 62.2, 55.6, 52.5, 52.2, 45.5, 39.3, 38.0, 35.8, 30.3.
(S)-Methyl 2-(2-benzyl-N-(4-methoxybenzyl)-4-oxopentanamido)-3-phenylpropanoate 114B

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with toluene (4 mL). Compound 113B (59 mg, 0.1 mmol), tributyltinhydride (0.05 mL, 0.2 mmol) and AIBN (5 mg, 0.03 mmol) were added to the flask in the indicated order. Then the solution was heated to 80 °C for 8 hours. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 5:1, Rf = 0.15) to give 29 mg (60%) of 114B as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 7.30-7.19 (m, 9H), 7.08-6.99 (m, 3H), 6.80 (d, 2H, J = 8.8 Hz), 4.51 (d, 1H, J = 16.0 Hz), 4.10 (dd, 1H, J = 6.0, 8.7 Hz), 3.87 (d, 1H, J = 16.0 Hz), 3.79 (s, 3H), 3.58 (s, 3H), 3.41-3.35 (m, 2H), 3.04 (dd, 1H, J = 8.6, 13.9 Hz), 2.94-2.87 (m, 2H), 2.61 (dd, 1H, J = 8.8, 13.4 Hz), 2.35 (dd, 1H, J = 5.0, 18.1 Hz), 2.06 (s, 3H); 13C (100 MHz, CDCl3) δ 207.3, 175.1, 171.1, 159.4, 139.0, 138.6, 129.6, 129.4, 128.8, 128.7, 114.1, 61.3, 55.5, 52.2, 52.0, 45.3, 39.4, 38.4, 35.6, 30.4.

(S)-Methyl 2-(2-benzyl-4-oxopentanamido)-3-phenylpropanoate 114C

A 10-mL round-bottomed flask was equipped with a stir bar and charged with acetonitrile (2 mL), water (0.5 mL), and compound 114A (50 mg, 0.1 mmol). To this solution was added ceric ammonium nitrate (0.25 g, 0.4 mmol) and the mixture was allowed to stir for 30 min under room temperature. To the solution was added water
(2 mL), and the solution was extracted with Et₂O (3 x 55 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1, Rᵢ = 0.10) yielded 23 mg (63%) of 114C as a viscous colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.11 (m, 8H), 6.80 (d, 2H, J = 9.5 Hz), 6.05 (d, 1H, J = 7.7 Hz), 4.79 (dd, 1H, J = 5.7, 11.5 Hz), 3.66 (s, 3H), 3.30-2.83 (m, 5H), 2.66 (dd, 1H, J = 5.3, 11.9 Hz), 2.50 (dd, 1H, J = 1.2, 11.6 Hz), 2.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 207.4, 173.9, 171.8, 139.2, 135.9, 129.4, 128.8, 128.8, 128.7, 127.2, 126.9, 53.2, 52.5, 45.7, 43.7, 38.3, 38.1, 30.4.

(S)-Methyl 2-(2-benzyl-4-oxopentanamido)-3-phenylpropanoate 114D

A 10-mL round-bottomed flask was equipped with a stir bar and charged with acetonitrile (2 mL), water (0.5 mL), and the γ-keto amide 114B (50 mg, 0.1 mmol). To this solution was added ceric ammonium nitrate (0.25 g, 0.4 mmol) and the mixture was allowed to stir for half hour under room temperature. The solution was diluted with water (2 mL), then extracted with Et₂O (3 x 55 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 1:1, Rᵢ = 0.15) yielded 22 mg (60%) of 114D as a viscous colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.12 (m, 10H), 6.02 (d, 1H, J = 7.8 Hz), 4.79 (dd, 1H, J = 1.2, 6.0 Hz), 3.64 (s, 3H), 3.07 (dd, 1H, J = 4.6, 13.8 Hz), 3.00 (dd, 1H, J = 6.2, 13.8 Hz),
2.93-2.84 (m, 3H), 2.64 (dd, 1H, J = 10.5, 16.2 Hz), 2.42 (d, 1H, J = 17.6 Hz), 2.06 (s, 3H).

b) Preparation of Peptide Isostere through C-Terminus

(5)-tert-Butyl 2-(3-(benzyloxy)-3-oxopropanoyl)pyrrolidine-1-carboxylate 119

A 50-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with compound 118 (2.12 g, 10 mmol), anhydrous tetrahydrofuran (15 mL) and 1,1-carbonyl diimidazole (1.7 g, 11 mmol) in the indicated order. In a separate 250-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (100 mL) and monobenzyl malonate (7.8 g, 40 mmol, in 10 mL of THF) in order. After the solution was cooled to 0 °C in the ice bath, dibutylmagnesium (1 M in heptanes, 20 mL, 20 mmol,) was added. After stirring for 10 minutes, the acyl imidazole solution was transferred to the magnesium salt solution using cannula. After stirring for 30 min, the reaction was quenched by cautious addition of 1 M HCl (25 mL). The solution was extracted with diethyl ether (3 x 50 mL) and the combined organic layers were washed by brine (50 mL). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo.

The residue was chromatographed on silica (hexanes:ethyl acetate = 6:1, Rf = 0.20) to yield 1.7 g (50%) of 119 as a colorless liquid mixture of two rotamers in a ratio of 1:1 with some minor enol forms present. 1H NMR (500 MHz, CDCl3) δ 7.41-7.30 (m,
5.23-5.13 (m, 2H), 4.41 (dd, 0.5H, J = 5.0, 8.3 Hz), 4.30 (dd, 0.5H, J = 5.6, 8.4 Hz), 3.67-3.41 (m, 2H), 3.66 (s, 2H), 2.27-1.86 (m, 4H), 1.48 (s, 9H); Both rotamers: $^{13}$C (125 MHz, CDCl$_3$) δ 202.8, 202.5, 167.1, 166.8, 166.5, 154.8, 153.8, 135.3, 128.6, 128.5, 128.4, 128.3, 128.2, 127.5, 126.9, 80.8, 80.2, 67.3, 67.2, 65.6, 65.2, 65.1, 48.9, 47.0, 46.8, 46.3, 45.3, 29.8, 28.5, 28.4, 28.3, 28.2, 24.5, 23.8. Resonances observed for the minor rotomer: $^1$H NMR (500 MHz, CDCl$_3$) δ 3.58 (s, 2H), 1.42 (s, 9H). Resonances observed for the enol forms: $^1$H NMR (500 MHz, CDCl$_3$) δ 12.0 (s, 1H), 4.71 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 195.1, 92.0.

(2S)-tert-Butyl 2-(4-(benzyloxy)-3-(hydroxymethyl)-4-oxobutanoyl)pyrrolidine-1-carboxylate

120A and 120B

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with methylene chloride (8 mL) and diethyl zinc (1.0 M in hexanes, 5.0 mL, 5.0 mmol). The solution was cooled to 0 °C and methylene iodide (0.4 mL, 5.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 119 (0.35 g, 1.0 mmol, in 0.5 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. Paraformaldehyde (0.2 g) was placed in a dry one-necked round-bottomed flask, which was capped with a rubber septum. One end of a cannula was inserted through the septum in the flask that contained paraformaldehyde, and the
other end of the cannula was inserted through the septum in the flask that contained
the zinc reagent. The paraformaldehyde flask was heated with a heat gun to induce
formation of formaldehyde, which was bubbled into the zinc-carbenoid solution for
10 minutes. After TLC analysis (hexanes:ethyl acetate = 6:1, \( R_f = 0.20 \)) indicated the
chain extension intermediate was consumed, the solution was quenched by cautious
addition of saturated aqueous ammonium chloride (5 mL). The solution was extracted
with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine
(10 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered
and concentrated under reduced pressure. The residue was chromatographed on silica
(hexanes:ethyl acetate = 4:1, \( R_f = 0.20 \)) to yield 0.29 g (75%) of \( 120A \) and \( 120B \) as a
colorless oil in a mixture of two isomers in a 1:1 ratio with some minor hemiacetal
forms present. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.37-7.29 (m, 10H), 5.20-5.08 (m, 4H),
4.92-4.66 (m, 2H), 4.44-4.20 (m, 2H), 3.91-3.71 (m, 4H), 3.64-3.36 (m, 4H),
3.31-3.13 (m, 2H), 3.03-2.71 (m, 2H), 2.17-1.78 (m, 8H); 1.46-1.38 (m, 18H); \(^{13}\)C
(100 MHz, CDCl\(_3\)) \( \delta \) 208.2, 207.5, 173.5, 172.9, 154.8, 153.8, 135.7, 135.5, 128.6,
128.5, 128.1, 109.0, 108.8, 89.7, 80.4, 80.1, 66.8, 66.7, 66.6, 65.1, 64.6, 62.6, 62.2,
46.9, 42.4, 42.1, 37.7, 37.2, 29.7, 28.7, 28.6, 28.4, 28.3, 24.4, 24.2, 23.6.
(2S)-tert-Butyl

2-(4-(benzyloxy)-3-((tert-butyldimethylsilyloxy)methyl)-4-oxobutanoyl)pyrrolidine-1-carboxylate 121A and 121B

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with N,N-dimethylformamide (5 mL), compound 120 (0.14 g, 0.36 mmol), tert-butyldimethylsilane (0.11 g, 0.72 mmol) and imidazole (48 mg, 0.72 mmol) in the indicated order. After being stirred overnight at room temperature, water (2 mL) was added to the mixture and the solution was extracted with diethyl ether (3 x 5 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 12:1; Rf = 0.20) to yield 0.14 g (75%) of 121A and 121B as a colorless oily mixture of configuration isomers and rotamers. $^1$H NMR (400 MHz, CDCl₃) δ 7.36-7.32 (m, 10H), 5.13-5.10 (m, 4H), 4.58-4.14 (m, 2H), 4.02-3.67 (m, 4H), 3.59-3.33 (m, 4H), 3.27-2.93 (m, 4H), 2.86-2.54 (m, 2H), 2.44-2.01 (m, 2H), 1.94-1.77 (m, 6H), 1.48-1.40 (m, 9H), 0.86 (s, 9H), 0.02-0.00 (m, 6H); $^{13}$C (100 MHz, CDCl₃) δ 213.7, 213.4, 178.6, 178.3, 160.1, 159.6, 141.4, 134.1, 134.0, 133.8, 133.7, 85.8, 85.6, 85.4, 85.3, 72.2, 71.2, 70.5, 70.0, 69.1, 68.9, 68.8, 52.5, 52.4, 52.3, 48.4, 48.2, 43.8, 43.1, 42.2, 35.4, 35.2, 34.0, 33.9, 31.4, 29.8, 29.3, 29.1, 23.8, 6.6, 0.1.
4-((S)-1-(tert-Butoxycarbonyl)pyrrolidin-2-yl)-2-((tert-butyldimethylsilyloxy)methyl)-4-oxobutanoic acid 122A and 122B

A 25-mL oven-dried, two-necked round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with methanol (5 mL), compound 121 (85 mg, 0.17 mmol, in 0.5 mL of methanol), and 10% Pd on carbon (10 mg) in the indicated order. After 10 minutes under nitrogen, the vessel was purged with hydrogen (in the main neck) via a balloon and the nitrogen inlet was removed from the other neck. The solution was allowed to stir at room temperature for overnight. Then the suspension was filtered and concentrated in vacuo to yield 67 mg (95%) of 122A and 122B as a colorless oily mixture of two isomers in a 1:1 ratio. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.37-4.17 (m, 2H), 3.89-3.67 (m, 4H), 3.56-3.31 (m, 4H), 3.13-2.86 (m, 4H), 2.69-2.57 (m, 2H), 2.16-1.76 (m, 8H); 1.41-1.36 (m, 18H), 0.82 (s, 18H), 0.00 (s, 12H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 214.3, 213.8, 183.4, 183.3, 159.6, 159.5, 86.0, 85.8, 71.0, 70.6, 70.1, 68.6, 52.5, 52.4, 52.3, 48.1, 47.9, 42.6, 41.9, 35.4, 35.3, 34.2, 34.1, 33.9, 31.4, 29.8, 29.3, 29.2, 23.8, 0.0.

(2S)-tert-Butyl

2-(3-((tert-butyldimethylsilyloxy)methyl)-4-((S)-1-methoxy-1-oxo-3-phenylpropan-2-ylamino)-4-oxobutanoyl)pyrrolidine-1-carboxylate 123A and 123B

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with compound 122 (66 mg,
0.16 mmol), *N,N*-dimethylformamide (3 mL), EDC (31 mg, 0.16 mmol), HOBt (22 mg, 0.16 mmol), phenylalanine methyl ester hydrochloride (36 mg, 0.16 mmol) and sodium bicarbonate (13 mg, 0.16 mmol) were added in the indicated order. The reaction was stirred at room temperature for overnight and diethyl ether (5 mL) was added to the solution. The organic phase was washed with 1M HCl (2 x 3 mL), brine (3 mL), sat. NaHCO₃ (2 x 3 mL) and brine (3 mL) in the indicated order. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 8:1) to yield 73 mg (79 %) of 123A (48%) and 123B (31%) as a mixture. 123A (two rotamers with a ratio of 1:1), one rotamer: ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.21 (m, 3H), 7.15 (d, 2H, *J* = 7.0 Hz), 7.02 (d, 1H, *J* = 7.9 Hz), 4.84 (m, 1H), 4.38 (dd, 1H, *J* = 4.3, 8.8 Hz), 3.76-3.58 (m, 2H), 3.68 (s, 3H), 3.53-3.40 (m, 2H), 3.09-2.89 (m, 4H), 2.50 (m, 1H), 2.12 (m, 1H), 2.04-1.81 (m, 3H), 1.45 (s, 9H), 0.84 (s, 9H), 0.07-0.00 (m, 6H); ¹³C (100 MHz, CDCl₃) δ 213.7, 213.4, 178.4, 178.1, 177.3, 160.2, 159.4, 141.7, 141.5, 134.9, 134.1, 132.6, 132.5, 85.6, 85.3, 70.5, 70.0, 69.3, 59.0, 58.9, 57.7, 52.5, 52.3, 48.9, 48.8, 43.8, 43.7, 43.6, 43.1, 34.3, 34.0, 33.9, 31.4, 30.0, 29.2, 23.8, 6.6, 5.6. Resonance observed for the other rotamer: ¹H NMR (400 MHz, CDCl₃) δ 6.85 (d, 1H, *J* = 7.8 Hz), 4.26 (dd, 1H, *J* = 4.8, 8.8 Hz), 3.65 (s, 3H), 1.41 (s, 9H), 0.84 (s, 9H). 123B (two rotamers with a ratio of 1:1), one rotamer: ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.19 (m, 3H), 7.13 (d, 2H, *J* = 7.0 Hz), 7.00 (d, 1H, *J* = 7.9 Hz), 4.82 (m, 1H), 4.36 (dd, 1H, *J* = 4.4, 8.7 Hz), 3.76-3.57 (m, 2H), 3.66 (s, 3H), 3.50-3.44 (m, 2H), 3.10-2.78 (m,
4H), 2.52 (m, 1H), 2.12 (m, 1H), 2.02-1.79 (m, 3H), 1.44 (s, 9H), 0.86 (s, 9H), 0.05-0.00 (m, 6H); $^{13}$C (100 MHz, CDCl$_3$) δ 213.7, 213.4, 178.1, 177.3, 159.4, 141.7, 134.9, 134.1, 134.0, 85.6, 85.3, 70.5, 69.3, 59.0, 57.7, 52.5, 43.8, 43.7, 35.4, 34.3, 34.0, 33.9, 31.4, 31.3, 31.2, 30.0, 29.4, 29.2, 23.7, 6.6. Resonance observed for the other rotamer: $^1$H NMR (400 MHz, CDCl$_3$) δ 6.84 (d, 1H, $J = 7.6$ Hz), 4.25 (dd, 1H, $J = 4.7, 8.7$ Hz), 3.64 (s, 3H), 1.39 (s, 9H), 0.82 (s, 9H).

(5)-Benzyl 4-(1,3-dioxoisindolin-2-yl)-5-methyl-3-oxohexanoate 128

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with compound 127 (0.11 g, 0.46 mmol), anhydrous tetrahydrofuran (5 mL) and 1,1-carbonyldiimidazole (80 mg, 0.5 mmol) in the indicated order. In a separate 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (8 mL) and monobenzyl malonate (0.36 g, 1.84 mmol) in order. After the solution was cooled to 0 °C in the ice bath, dibutylmagnesium (1 M in heptanes, 0.92 mL, 1.84 mmol,) was added. After stirring for 10 minutes, the acyl imidazole solution was transferred to the magnesium salt solution using cannula. After stirring for 30 min, the reaction was quenched by cautious addition of 1 M HCl (5 mL). The solution was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed by brine (10 mL). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in
The residue was chromatographed on silica (hexanes:ethyl acetate = 10:1, $R_f = 0.20$) to yield 95 mg (55%) of 128 as a colorless liquid with some minor enol forms present. (NMR spectrum available in the CD)

$\text{(LR,4S,10bS)-Benzyl}$

$\textcolor{red}{10b-hydroxy-4-isopropyl-3,6-dioxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindole-1-carboxylate 130}$

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with methylene chloride (4 mL) and diethyl zinc (1.0 M in hexanes, 0.5 mL, 0.5 mmol). The solution was cooled to 0 °C and methylene iodide (0.04 mL, 0.5 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 128 (38 mg, 0.1 mmol, in 0.5 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. After TLC analysis (hexanes:ethyl acetate = 10:1, $R_f = 0.20$) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (2 x 5 mL), washed with brine (10 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 5:1, $R_f = 0.10$) to yield 22 mg (58%) of 130 as a white solid. (NMR spectrum attached)
(S)-2-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)propanoic acid 136

A 100-mL round-bottomed flask was equipped with a stir bar and charged with water (40 mL), compound 132 (4.0 g, 20 mmol) and sodium hydroxide (1.6 g, 40 mmol) in the indicated order. After stirring for 10 min, the solution was cooled to 0 °C using ice bath and benzyl chloroformate (3.6 mL, 25 mmol) was add dropwise to it. The mixture was warmed to room temperature and allowed to stir for 1 hour. After being extracted with diethyl ether (3 x 10 mL), the solution was brought to pH = 1.0 with cautious addition of conc. HCl, and then extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried carefully over anhydrous sodium sulfate and concentrated in vacuo to yield 6.5 g (95%) of 136 as a colorless oily mixture of two rotamers with a ratio of 1:1. ¹H NMR (400 MHz, CDCl₃) δ 10.4 (broad, 1H, OH), 7.35-6.84 (m, 9H), 5.20 (m, 2H, J = 1.8 Hz), 4.64-4.18 (m, 3H), 3.79 (s, 3H), 1.42-1.34 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 177.7, 177.5, 159.1, 156.6, 136.4, 136.3, 130.1, 129.9, 129.6, 128.8, 128.7, 128.5, 128.3, 128.1, 114.2, 68.0, 67.9, 55.6, 55.5, 55.1, 50.9, 49.9, 16.1, 15.4.

(S)-Allyl 4-((benzyloxycarbonyl)(4-methoxybenzyl)amino)-3-oxopentanoate 137

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with compound 136 (1.3 g, 3.8 mmol), anhydrous tetrahydrofuran (10 mL) and 1,1-carbonyldiimidazole (0.64 g, 4.0 mmol) in the indicated order. In a separate 100-mL oven-dried, round-bottomed flask,
equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (40 mL) and monoallyl malonate (2.18 g, 15.2 mmol, in 5 mL of THF) in order. After the solution was cooled to 0 °C in the ice bath, dibutylmagnesium (1 M in heptanes, 7.6 mL, 15.2 mmol,) was added. After stirring for 10 minutes, the acyl imidazole solution was transferred to the magnesium salt solution using cannula. After stirring for 30 min, the reaction was quenched by cautious addition of 1 M HCl (10 mL). The solution was extracted with diethyl ether (3 x 25 mL) and the combined organic layers were washed by brine (25 mL). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 7:1, Rf = 0.20) to yield 1.4 g (84%) of 137 as a colorless liquid mixture of two rotamers in a ratio of 1:1. One rotamer: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.27-7.05 (m, 7H), 6.79-6.73 (m, 2H), 5.77 (m, 1H), 5.28-5.03 (m, 4H), 4.60-4.23 (m, 3H), 4.04 (m, 1H), 3.74 (m, 1H), 3.71 (s, 3H), 3.35 (d, 1H, $J = 18.2$ Hz), 3.22 (d, 1H, $J = 15.8$ Hz), 1.19 (d, 3H, $J = 7.2$ Hz); $^{13}$C (100 MHz, CDCl$_3$) δ 200.7, 167.4, 167.1, 159.6, 159.4, 156.0, 136.3, 135.8, 130.3, 129.6, 128.8, 128.6, 128.4, 118.9, 114.3, 68.1, 61.8, 61.6, 55.5, 51.4, 50.3, 45.3, 44.8, 13.9, 13.3. Resonances observed for the other rotamer: $^1$H NMR (400 MHz, CDCl$_3$) δ 3.85 (m, 1H), 3.14 (d, 1H, $J = 16.0$ Hz), 3.05 (d, 1H, $J = 15.9$ Hz), 1.14 (d, 3H, $J = 6.7$ Hz).
(S)-Allyl

5-((benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-(hydroxymethyl)-4-oxohexanoate 138A and 138B

A 50-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with methylene chloride (15 mL) and diethyl zinc (1.0 M in hexanes, 10.0 mL, 10.0 mmol). The solution was cooled to 0 °C and methylene iodide (0.80 mL, 10.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 137 (0.85 g, 2.0 mmol, in 1 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. Paraformaldehyde (0.4 g) was placed in a dry one-necked round-bottomed flask, which was capped with a rubber septum. One end of a cannula was inserted through the septum in the flask that contained paraformaldehyde, and the other end of the cannula was inserted through the septum in the flask that contained the zinc reagent. The paraformaldehyde flask was heated with a heat gun to induce formation of formaldehyde, which was bubbled into the zinc-carbenoid solution for 10 minutes. After TLC analysis (hexanes:ethyl acetate = 7:1, Rf = 0.10) indicated the chain extension intermediate was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (10 mL). The solution was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (15 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was

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chromatographed on silica (hexanes:ethyl acetate = 4:1, \( R_f = 0.20 \)) to yield 0.74 g (79%) of 138A and 138B as a colorless oil in a mixture of two isomers in a 1:1 ratio. \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.31-7.10 (m, 7H), 6.83-6.75 (m, 2H), 5.84 (m, 1H), 5.28-5.09 (m, 4H), 4.73-3.32 (m, 5H), 3.71 (s, 3H), 3.16-1.97 (m, 6H), 1.28-0.85 (m, 3H); \(^13\)C (100 MHz, CDCl₃) \( \delta \) 206.7, 206.6, 206.5, 173.6, 173.4, 159.4, 159.3, 156.3, 156.2, 136.4, 136.2, 129.4, 129.2, 128.7, 128.4, 128.2, 118.4, 114.2, 68.0, 66.4, 65.8, 65.6, 62.7, 62.4, 61.9, 61.7, 55.5, 50.4, 50.0, 43.0, 37.1, 37.0, 14.5, 14.2, 13.8, 13.5.

\((S,S)\)-Allyl

5-((benzylloxycarbonyl)(4-methoxybenzyl)amino)-2-((tert-butyldiphenylsilyloxy)methyl)-4-oxohexanoate 139A and 139B

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with \( N,N \)-dimethylformamide (5 mL), compound 138 (0.30 g, 0.64 mmol), tert-butylchlorodiphenylsilane (0.36 mL, 1.4 mmol) and imidazole (0.10 g, 1.4 mmol) in the indicated order. After stirred for overnight at room temperature, water (3 mL) was added to the mixture and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 16:1; \( R_f = 0.20 \)) to yield 0.32 g (71%) of 139A and 139B as a colorless oily mixture of two isomers with a ratio of 1:1. \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.64-7.60 (m, 8H), 7.43-7.23 (m, 27 H), 7.20-7.10 (m, 7H), 6.75-6.65 (m, 2H), 5.85-5.75 (m, 1H), 5.75-5.65 (m, 4H), 4.69-3.31 (m, 5H), 3.66 (s, 3H), 3.16-1.87 (m, 6H), 1.28-0.87 (m, 3H); \(^13\)C (100 MHz, CDCl₃) \( \delta \) 206.7, 206.6, 206.5, 173.6, 173.4, 159.4, 159.3, 156.3, 156.2, 136.4, 136.2, 129.4, 129.2, 128.7, 128.4, 128.2, 118.4, 114.2, 68.0, 66.4, 65.8, 65.6, 62.7, 62.4, 61.9, 61.7, 55.5, 50.4, 50.0, 43.0, 37.1, 37.0, 14.5, 14.2, 13.8, 13.5.

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6.80 (s, 3H), 5.86 (m, 2H), 5.31-5.07 (m, 8H), 4.66-4.17 (m, 7H), 3.92-3.64 (m, 3H),
3.74 (s, 6H), 3.11-1.78 (m, 6H), 1.26-1.17 (m, 6H), 1.06 (s, 9H), 1.02 (s, 9H); $^{13}$C
(100 MHz, CDCl$_3$) $\delta$ 206.9, 206.5, 173.2, 173.1, 172.9, 159.4, 159.3, 159.1, 156.4,
156.1, 135.8, 133.4, 132.3, 130.0, 129.3, 128.9, 128.5, 128.3, 128.2, 128.0, 118.4,
114.2, 67.8, 65.7, 64.7, 64.4, 62.0, 61.6, 55.4, 50.2, 49.7, 43.6, 43.2, 37.7, 37.6, 37.4,

(5S)-5-((Benzyloxycarbonyl)(4-methoxybenzyl)amino)-2-((tert-butylidiphenylsilyl
oxy)methyl)-4-oxohexanoic acid 140A and 140B

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of
nitrogen through a needle and a stir bar, was charged with terahydrofuran (4 mL),
compound 139 (0.30 g, 0.42 mmol, in 0.8 mL of tetrahydrofuran), pyrrolidine (0.33
mL) and tetrakis(triphenylphosphine)-palladium (25 mg) in the indicated order. The
solution was allowed to stir at room temperature for 30 minute. Then the suspension
was filtered and concentrated in vacuo. The residue was chromatographed on silica
(hexanes:ethyl acetate = 3:1; $R_f = 0.20$) to yield 0.24 g (80%) of 140A and 140B as a
oily mixture of two isomers with a ratio of 1:1. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$
7.69-7.07 (m, 16H), 6.79 (s, 3H), 5.20-4.77 (m, 3H), 4.54 (m, 1H), 4.18 (m, 1H),
3.92-3.50 (m, 2H), 3.74 (s, 3H), 3.34-2.65 (m, 3H), 2.16 (m, 1H), 1.27-1.17 (m, 3H),
1.06-1.01 (m, 9H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 205.5, 175.5, 158.0, 155.1, 154.8, 134.4,
131.6, 131.1, 131.0, 130.6, 128.8, 128.0, 127.6, 127.4, 127.1, 126.9, 126.8, 112.9,
(2S)-Methyl 2-((5S)-5-((benzyloxy carbonyl)(4-methoxybenzyl)amino)-2-((tert-butyldiphenylsilyloxy)methyl)-4-oxohexanamido)propanoate 141A and 141B

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with compound 140 (87 mg, 0.13 mmol), N,N-dimethylformamide (3 mL), EDC (27 mg, 0.13 mmol), HOBt (19 mg, 0.13 mmol), alanine methyl ester hydrochloride salt (19 mg, 0.13 mmol) and sodium bicarbonate (11 g, 0.13 mmol) were added in the indicated order. The reaction was stirred at room temperature for overnight and diethyl ether (5 mL) was added to the solution. The organic phase was washed with 1M HCl (2 x 3 mL), brine (3 mL), sat. NaHCO₃ (2 x 3 mL) and brine (3 mL) in the indicated order. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 5:1; Rᵣ = 0.10) to yield 0.23 g (73%) of 141A and 141B as a colorless oily mixture of two isomers with a ratio of 1:1. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (b, 8H), 7.43-7.38 (m, 12 H), 7.30-7.10 (m, 13H), 6.89-6.79 (m, 5H), 5.21-4.96 (m, 4H), 4.63-4.05 (m, 8H), 3.92-3.50 (m, 2H), 3.95-3.34 (m, 4H), 3.75 (s, 6H), 3.70 (s, 6H), 3.02 (m, 1H), 2.88-2.37 (m, 3H), 2.20 (m, 1H), 1.86 (m, 1H), 1.38-1.36 (m, 6H), 1.26-1.12 (m, 6H), 1.06 (s, 18H); ¹³C (100
MHz, CDCl₃) δ 206.7, 173.4, 172.9, 172.8, 159.3, 159.1, 156.2, 156.0, 135.8, 133.0, 130.1, 129.9, 129.4, 129.0, 128.7, 128.3, 128.1, 114.2, 67.8, 65.0, 64.8, 62.4, 62.2, 61.7, 55.4, 52.5, 51.7, 51.2, 50.7, 50.0, 48.4, 44.4, 44.3, 43.9, 37.5, 37.2, 37.0, 27.0, 19.4, 18.6, 14.7, 14.4, 14.0, 13.7.

(S)-Benzyl 2-(tert-butoxycarbonylamino)-4-(dimethylamino)-4-oxobutanoate 143

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with compound 142 (0.32 g, 1.0 mmol) N,N-dimethylformide (5 mL), EDC (0.20 g, 1.0 mmol), HOBT (0.15 g, 1.0 mmol), N,N-dimethylamine hydrochloride salt (81 mg, 1.0 mmol) and sodium bicarbonate (84 mg, 1.0 mmol) were added in the indicated order. The reaction was stirred at room temperature for overnight and diethyl ether (3 mL) was added to the solution. The organic phase was washed with 1M HCl (2 x 3 mL), brine (3 mL), sat. NaHCO₃ (2 x 3 mL) and brine (3 mL) in the indicated order. The resulting liquid was filtered and concentrated under reduced pressure to yield 0.31 g (90%) of 143 as colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.89 (d, 1H, -NH, J = 9.3 Hz), 5.17 (d, 1H, J = 12.5 Hz), 5.11 (d, 1H, J = 12.4 Hz), 4.58 (m, 1H), 3.11 (dd, 1H, J = 4.0, 16.7 Hz), 2.90 (s, 3H), 2.86 (s, 3H), 2.73 (dd, 1H, J = 4.0, 16.7 Hz), 1.39 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 171.6, 170.1, 155.8, 135.7, 128.4, 128.0, 127.9, 79.6, 66.9, 50.2, 37.0, 35.7, 35.1, 28.3.

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(S)-3-(4-Benzyl-2-oxooxazolidin-3-yl)-3-oxopropanoic acid 149

A 25-mL oven-dried, two-necked round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with compound 152 (50 mg, 0.20 mmol), methanol (6 mL), and 10 % Pd on carbon (15 mg) in the indicated order. The vessel was purged with hydrogen and the nitrogen was removed. The suspension was allowed to stir at room temperature for overnight. The suspension was filtered and concentrated in vacuo to yield 50 mg (95%) of 149 as a colorless oil.

\[ ^1H \text{ NMR (500 MHz, CD}_3\text{OD) } \delta 7.37-7.27 \text{ (m, 5H), 4.70 (m, 1H), 4.35 (dd, 1H, } J = 8.9, 8.9 \text{ Hz), 4.27 (dd, 1H, } J = 2.5, 8.9 \text{ Hz), 3.35 (s, 2H), 3.22 (dd, 1H, } J = 3.2, 13.8 \text{ Hz), 2.99 (dd, 1H, } J = 8.1, 13.5 \text{ Hz); } ^13\text{C NMR (100 MHz, CD}_3\text{OD) } \delta 171.2, 165.9, 153.8, 135.2, 129.7, 129.2, 127.6, 66.8, 55.3, 42.8, 37.7. \]

1,3-Bis((S)-4-Benzyl-2-oxooxazolidin-3-yl)-2-chloropropane-1,3-dione 150

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with compound 148 (0.25 g, 1.0 mmol), toluene (5 mL), Meldrum’s acid (0.22 g, 1.5 mmol), copper (II) chloride (0.20 g, 1.5 mmol), and copper powder (64 mg, 1.0 mmol) were added in the indicated order. The mixture was heated at reflux for overnight. After cooling to room temperature, the solution was filtered and concentrated in vacuo to yield 0.2 g (43%) of 150. \[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{) } \delta 7.35 \text{ (d, 2H, } J = 7.8 \text{ Hz), 7.34 (d, 2H, } J = 7.2 \text{ Hz), 7.27 (m, 4H), 7.23 (d, 2H, } J = 7.2 \text{ Hz), 6.94 (s, 1H), 4.78 (m, 1H), 4.70 (m, 1H), \]

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4.34 (dd, 1H, J = 8.9, 17.4 Hz), 4.29-4.22 (m, 3H), 3.45 (dd, 1H, J = 3.2, 13.6 Hz), 3.32 (dd, 1H, J = 3.4, 13.6 Hz), 2.86 (dd, 1H, J = 9.3, 13.6 Hz), 2.78 (dd, 1H, J = 9.2, 13.6 Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 163.9, 163.2, 153.3, 153.0, 135.1, 134.6, 129.5, 129.1, 127.6, 127.4, 67.1, 66.8, 57.6, 56.0, 55.1, 37.5, 37.1.

(S)-Benzyl 3-(4-benzyl-2-oxooxazolidin-3-yl)-3-oxopropanoate 152

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with (S)-4-benzyloxazolidin-2-one (0.18 g, 1.0 mmol), dichloromethane (5 mL), triethylamine (0.23 mL, 1.5 mmol), and 4-dinethylaminopyridine (12 mg, 0.1 mmol), were added in the indicated order. After cooling to 0 °C, malonic acid monobenzyl ester chloride (0.56 g, 2.0 mmol, in 2 mL of dichloromethane) was added in one portion and the solution was allowed to stir for overnight and diethyl ether (10 mL) was added to the solution. The organic phase was washed with 1M HCl (2 x 5 mL), brine (5 mL), sat. NaHCO\(_3\) (2 x 5 mL) and brine (5 mL) in the indicated order. The resulting liquid was filtered and concentrated under reduced pressure to yield 0.21 g (60%) of 152 as colorless oil. \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.27 (m, 8H), 7.19 (d, 2H, J = 8.2 Hz), 5.18 (d, 2H, J = 3.3 Hz), 4.67 (m, 1H), 4.20-4.11 (m, 2H), 4.06 (d, 1H, J = 16.5 Hz), 4.00 (d, 1H, J = 16.5 Hz), 3.32 (dd, 1H, J = 3.3, 13.5 Hz), 2.65 (dd, 1H, J = 9.9, 13.5 Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 166.8, 165.8, 153.7, 135.3, 129.6, 129.2, 128.8, 128.7, 127.6, 67.6, 66.6, 55.3, 43.2, 37.7.
Benzyl

(R)-5-((S)-4-benzyl-2-oxooxazolidin-3-yl)-3,5-dioxopentan-2-yl(4-methoxybenzyl) carbamate 154

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with anhydrous tetrahydrofuran (4 mL), compound 136 (0.40 g, 1.0 mmol, in 1 mL of tetrahydrofuran), and 1,1-dicarbonyl imidazole (0.18 g, 1.1 mmol) in the indicated order. In a separate 50-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (15 mL) and diisopropylamine (0.56 mL, 4 mmol) in order. After the solution was cooled to 0 °C in the ice bath, n-BuLi (2 M in hexanes, 2 mL, 4 mmol) was added. After stirring for 10 min, the reaction mixture was cooled to -78 °C, compound 153 (0.88 g, 4.0 mmol, in 5 mL of THF) was added in half hour using syringe pump. The acyl imidazole solution was transferred to the enolate solution using cannula. After stirring for half hour at -78 °C, the reaction was quenched by cautious addition of 1 M HCl (5 mL). The solution was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed by brine (5 mL). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1; Rf = 0.30) to yield 0.46 g (85%) of 154 a colorless oily mixture of two rotamers with a ratio of 1:1. 1H NMR (400 MHz, CDCl3) δ 7.35-7.16 (m, 12H), 6.86-6.81 (m, 2H), 5.24-5.12 (m, 2H),
4.71-4.59 (m, 2H), 4.36-4.04 (m, 5H), 3.93 (d, 0.5H, $J = 16.6$ Hz), 3.75 (s, 3H), 3.60 (d, 0.5H, $J = 16.5$ Hz), 3.24 (dd, 1H, $J = 14.0, 14.0$ Hz), 2.74 (m, 1H), 1.30 (2d, 3H, $J = 6.5$ Hz and $J = 6.5$ Hz), 1.22 (d, 3H, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$

201.2, 166.8, 159.2, 155.8, 153.6, 153.1, 135.1, 130.1, 129.6, 129.5, 129.4, 129.3, 129.0, 128.6, 128.4, 128.2, 128.1, 127.4, 114.0, 67.9, 67.8, 66.4, 66.1, 61.9, 60.4, 55.2, 55.1, 55.0, 54.9, 51.6, 51.4, 50.3, 47.4, 47.3, 47.1, 37.8, 37.7, 37.6, 23.8, 21.0, 14.2, 13.9, 13.2.

**Benzyl**

**(2R)-4-(2-(5)-4-benzyl-2-oxooxazolidin-3-yl)-2-hydroxycyclopropyl)-3-oxobutan-2-yl(4-methoxybenzyl)carbamate 159**

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (4 mL) and diethyl zinc (1.0 M in hexanes, 1.5 mL, 1.5 mmol). The solution was cooled to 0 °C in the ice bath and diiodomethane (0.12 mL, 1.5 mmol) was added dropwise. After stirring for 10 min, compound 154 (0.20 mmol, in 0.5 mL of dichloromethane) was added to the resulting white suspension in order. The mixture was stirred for 1 hour. After TLC analysis (hexanes:ethyl acetate = 3:1; $R_f = 0.30$) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (4 mL) and the mixture extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (5 mL), and dried over
anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 1:1; \( R_f = 0.20 \)) to yield 74 mg (65%) of 159 as a colorless oily mixture of two rotamers with a ratio of 1:1. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.40-7.15 (m, 12H), 6.82 (s, 2H), 5.10 (s, 2H), 4.76 (d, 1H, \( J = 15.4 \) Hz), 4.21-4.12 (m, 2H), 4.05-3.96 (m, 3H), 3.78 (s, 3H), 3.44 (m, 1H), 2.71-2.49 (m, 3H), 1.58 (m, 1H), 1.39-1.21 (m, 4H), 0.95 (m, 1H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 207.9, 159.4, 157.4, 156.6, 136.8, 136.0, 130.1, 129.8, 129.7, 129.5, 129.4, 129.2, 128.8, 128.5, 128.3, 127.0, 114.3, 68.3, 66.6, 64.7, 61.4, 57.7, 55.5, 50.3, 39.4, 37.1, 22.1, 20.1, 13.3.

**Benzyl 5-oxo-2-phenyltetrahydrofuran-3-carboxylate 166**

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with methylene chloride (3 mL) and diethyl zinc (1.0 M in hexanes, 1.0 mL, 1.0 mmol). The solution was cooled to 0 °C and methylene iodide (0.08 mL, 1.0 mmol) was added slowly by syringe. After stirring for 10 minutes, compound 152 (70 mg, 0.20 mmol, in 0.5 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes, at which time freshly distilled benzaldehyde (0.03 g, 0.3 mmol) was added into the reaction mixture by syringe. After TLC analysis (hexanes:ethyl acetate = 5:1, \( R_f = 0.20 \)) indicated the chain extension intermediate was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium

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chloride (1 mL). The mixture was extracted with diethyl ether (2 x 5 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The organic solution was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexane:ethyl acetate = 1:1, \( R_f = 0.25 \)) to yield XX g (XX%) of 166.

**Benzyl**

\((2R,5R)-6-((S)-4-benzyl-2-oxooxazolidin-3-yl)-5-(hydroxymethyl)-3,6-dioxohexan-2-yl(4-methoxybenzyl)carbamate 167\)

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (4 mL) and diethyl zinc (1.0 M in hexanes, 1.5 mL, 1.5 mmol). The solution was cooled to 0 °C in the ice bath and diiodomethane (0.12 mL, 1.5 mmol) was added dropwise. After stirring for 10 min, paraformaldehyde (0.5 g, 6 mmol) and compound 159 (0.20 mmol, in 0.5 mL of dichloromethane) were added to the resulting white suspension in order. The mixture was stirred for 1 hour. After TLC analysis (hexanes:ethyl acetate = 3:1; \( R_f = 0.30 \)) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (4 mL) and the mixture extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was
chromatographed on silica (hexanes:ethyl acetate = 1:1; R_f = 0.25) to yield 83 mg (71%) of 167 as a colorless oily mixture of two rotamers with a ratio of 1:1, with some minor hemiacetal form. ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.14 (m, 12H), 6.88-6.79 (m, 2H), 5.34-5.10 (m, 2H), 4.78-4.04 (m, 7H), 3.78 (s, 3H), 3.60 (m, 1H), 3.22 (m, 1H), 3.02-2.72 (m, 2H), 2.59-2.11 (m, 2H), 1.29-1.26 (m, 3H); ^13C NMR (100 MHz, CDCl_3) δ 206.1, 205.7, 172.9, 172.8, 158.2, 158.0, 157.7, 156.7, 154.9, 153.0, 152.1, 135.2, 134.2, 134.0, 133.9, 129.3, 128.9, 128.7, 128.4, 128.0, 127.8, 127.6, 127.4, 127.0, 126.8, 126.4, 126.3, 113.0, 112.9, 112.7, 66.7, 66.5, 62.7, 60.2, 54.4, 54.2, 50.2, 48.7, 42.5, 40.4, 40.0, 37.0, 36.9, 36.6, 13.2, 12.9, 12.7. Hemiacetal: ^13C NMR (100 MHz, CDCl_3) 107.0, 106.7.

(5)-4-Benzyl-3-((R)-5-oxotetrahydrofuran-3-carbonyl)oxazolidin-2-one 169

A 25-mL round-bottom flask was equipped with a stir bar and charged with THF (10 mL), water (2.5 mL), and compound 167 (0.11 g, 0.2 mmol). To this solution was added ceric ammonium nitrate (0.43 g, 0.8 mmol) and the mixture was allowed to stir for 30 min under room temperature. The solution was added water (5.0 mL), then extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1; R_f = 0.20) yielded 0.15 g (70%) of 169 as a viscous colorless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.36-7.17 (m, 5H), 4.71 (m, 1H), 4.68 (m, 1H), 4.62 (t, 3H, J = 7.9 Hz), 4.42-4.26 (m, 4H), 3.24 (dd,
1H, J = 3.3, 13.6 Hz), 3.03 (dd, 1H, J = 5.1, 17.7 Hz), 2.88 (dd, 1H, J = 9.1, 13.5 Hz), 2.72 (dd, 1H, J = 9.1, 17.9 Hz); 13C NMR (125 MHz, CDCl3) δ 175.4, 170.7, 153.3, 134.6, 129.4, 129.1, 127.7, 69.3, 67.0, 55.2, 40.1, 37.8, 30.1.

(R)-5-Ootetrahydrofuran-3-carboxylic acid 170

A 10-mL round-bottom flask was equipped with a stir bar and charged with THF (4.0 mL), water (1 mL), and compound 169 (26 mg, 0.09 mmol). To this solution was added lithium hydroxide monohydrate (9 mg, 0.2 mmol) and hydrogen peroxide (35 wt. % in water, 0.02 mL, 0.2 mmol). The mixture was allowed to stir for 1 hour under room temperature and extracted with Et2O (3 x 5 mL). The solution was brought to pH = 1.0 with conc. HCl, then extracted with ethyl acetate (5 x 5 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo to yield 7 mg (60%) of 170. ([α]25D = + 40.0 (c = 0.001 g/mL, MeOH)). 1H NMR (500 MHz, CDCl3) δ 4.59-4.49 (m, 2H), 3.52 (m, 1H), 2.90 (dd, 1H, J = 7.0, 17.9 Hz), 2.80 (dd, 1H, J = 9.7, 17.9 Hz); 13C NMR (125 MHz, CDCl3) δ 174.7, 174.7, 68.7, 39.6, 30.7.
(S)-Benzyl

2-(3-((S)-5-benzyl-2-oxooxazolidin-3-yl)-3-oxopropanoyl)pyrrolidine-1-carboxylate 171

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with (S)-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid (0.25 g, 0.5 mmol, in 1 mL of tetrahydrofuran), anhydrous tetrahydrofuran (3 mL) and 1,1-dicarbonyl imidazole (0.17 g, 1.1 mmol) in the indicated order. In a separate 50-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (15 mL) and diisopropyl amine (0.56 mL, 4 mmol) in order. After the solution was cooled to 0 °C in the ice bath, n-BuLi (2 M in hexanes, 2.0 mL, 4.0 mmol) was added. After stirring for 10 min, the reaction mixture was cooled to -78 °C, compound 153 (0.88 g, 4.0 mmol, in 3 mL of THF) was added in half hour using syringe pump. The acyl imidazole solution was transferred to the enolate solution using cannula. After stirring for half hour, the reaction was quenched by cautious addition of 5 mL 1 M HCl solution. The solution was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed by brine (5 mL). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 4:1; Rf = 0.20) to yield 0.36 g (80%) of 171 a colorless oily mixture of two rotamers with a ratio of 1:1. $^1$H NMR (400 MHz, CDCl$_3$) δ
7.37-7.20 (m, 20H), 5.18-5.08 (m, 4H), 4.73-4.67 (m, 2H), 4.50 (dd, 1H, J = 3.4, 8.1 Hz), 4.42 (dd, 1H, J = 4.5, 8.3 Hz), 4.31-4.04 (m, 8H), 3.72-3.47 (m, 4H), 3.36 (d, 2H, J = 13.5 Hz), 2.86-2.74 (m, 2H), 2.28-1.85 (m, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 201.1, 165.4, 165.2, 154.3, 153.4, 152.6, 152.5, 135.5, 135.2, 135.1, 128.4, 127.9, 127.5, 127.2, 126.8, 126.3, 66.4, 66.2, 65.3, 64.2, 64.0, 54.0, 47.3, 46.7, 46.3, 45.8, 36.6, 28.6, 27.3, 23.3, 22.5.

(S)-benzyl

2-((R)-4-((S)-5-benzyl-2-oxooxazolidin-3-yl)-3-(hydroxymethyl)-4-oxobutanoyl)p
yrrolidine-1-carboxylate 172

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (6 mL) and diethyl zinc (1.0 M in hexanes, 1.5 mL, 1.5 mmol). The solution was cooled to 0 °C in the ice bath and diiodomethane (0.12 mL, 1.5 mmol) was added dropwise. After stirring for 10 min, paraformaldehyde (0.2 g, 2.2 mmol) and compound 171 (0.15 g, 0.3 mmol, in 0.5 mL of dichloromethane) were added to the resulting white suspension in order. The mixture was stirred for 1 hour. After TLC analysis (hexanes:ethyl acetate = 4:1; $R_f = 0.20$) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (5 mL) and the mixture extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (5 mL), and dried over
anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 2:1; \( R_f = 0.20 \)) to yield 0.10 g (70%) of 172 a colorless oily mixture of two rotamers with a ratio of 1:1. \(^1\)H NMR (400 MHz, \( CDCl_3 \)) \( \delta \): 7.38-7.18 (m, 10H), 5.24-5.01 (m, 2H), 4.66 (m, 1H), 4.38-3.98 (m, 5H), 3.79-3.56 (m, 2H), 3.27-2.96 (m, 2H), 2.79 (m, 2H), 2.50 (m, 1H), 2.21-1.86 (m, 4H); \(^1\)3C NMR (100 MHz, \( CDCl_3 \)) 209.1, 208.9, 175.0, 155.5, 154.6, 154.2, 153.4, 136.8, 135.4, 135.3, 129.7, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6, 128.3, 128.1, 127.6, 67.4, 67.3, 67.2, 66.6, 65.9, 65.4, 63.8, 63.7, 55.6, 47.6, 41.6, 41.2, 38.2, 38.1, 37.9, 37.5, 30.2, 29.2, 24.8, 24.0. two rotamers:
Hemiceral: \(^1\)3C NMR (100 MHz, \( CDCl_3 \)) 109.1.

(S)-Benzyl

2-((2R,4R)-4-(\((S)-4\)-benzyl-2-oxooxazolidine-3-carbonyl)tetrahydrofuran-2-yl)pyrrolidine-1-carboxylate 173A and 173B

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (3 mL), compound 172 (74 mg, 0.15 mmol). After the solution was cooled to the -78 °C, triethylsilane (0.1 mL, 0.5 mmol) and boron trifluoride diethyl etherate (0.05 mL, 0.5 mmol) were added dropwise in the indicated order. The reaction solution was left stirring for forty minutes at -78 °C and two hours at room temperature. The solution was quenched with saturated sodium bicarbonate solution (2 mL), extracted with
diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous sodium sulfate and concentrated in vacuo. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 2:1, Rf = 0.20) to offer 83 mg (69%) of 173A and 173B as a mixture of two isomers in a 1:1 ratio. \( ^1H \) NMR (500 MHz, CDC\textsubscript{3}) \( \delta \) 7.39-7.16 (m, 10H), 5.19-5.06 (m, 2H), 4.66 (m, 1H), 4.28-3.85 (m, 7H), 3.62 (m, 1H), 3.40 (m, 1H), 3.26 (m, 1H), 2.76 (m, 1H), 2.32-1.70 (m, 6H); \( ^{13}C \) (100 MHz, CDC\textsubscript{3}) \( \delta \) 173.4, 172.2, 154.4, 152.3, 152.2, 135.9, 134.0, 81.1, 80.2, 79.4, 69.6, 69.1, 65.8, 65.6, 65.3, 59.1, 58.6, 57.4, 54.5, 54.2, 46.0, 45.8, 43.0, 42.8, 36.8, 31.0, 27.0, 24.9, 23.0.

(4S)-4-Benzyl-3-((3R)-5-(pyrrolidin-2-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one 174A and 174B

A 25-mL oven-dried, two-necked round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with compound 173 (30 mg, 0.06 mmol), methanol (6 mL), and 10 % Pd on carbon (8 mg) in the indicated order. The vessel was purged with hydrogen and the nitrogen was removed. The suspension was allowed to stir at room temperature for overnight. The suspension was filtered and concentrated in vacuo to yield 17 mg (80%) of 174A and 174B as a mixture of two isomers in a 1:1 ratio. \( ^1H \) NMR (500 MHz, CDC\textsubscript{3}) \( \delta \) 7.23-7.11 (m, 10H), 4.67-4.63 (m, 2H), 4.26 (m, 1H), 4.20 (m, 1H), 4.16-4.05 (m, 3H), 3.97 (m, 1H), 3.90 (m, 1H), 3.81 (m, 1H), 3.49 (m, 1H), 3.00 (m, 1H), 2.92 (m, 1H), 2.77 (d, 1H, J
= 3.7 Hz), 2.49 (m, 1H), 2.20 (m, 1H), 2.13-1.89 (m, 5H), 1.76 (m, 1H), 1.66 (m, 1H);

$^{13}$C (100 MHz, CDCl$_3$) $\delta$ 174.0, 173.0, 154.2, 154.1, 135.6, 129.5, 128.6, 127.1, 79.2, 77.9, 71.4, 70.8, 67.0, 66.8, 63.6, 61.9, 55.3, 55.1, 46.0, 45.4, 44.1, 37.2, 37.0, 31.8, 29.5, 26.7, 25.0, 24.0, 23.6.

**Benzyl 5-oxotetrahydrofuran-3-carboxylate 177**

A 5-mL round-bottomed flask was equipped with a stir bar and charged with acetonitrile (2 mL), water (0.5 mL), and compound 176 (50 g, 0.1 mmol). To this solution was added ceric ammonium nitrate (0.21 g, 0.4 mmol) and the mixture was allowed to stir for 30 min under room temperature. The solution was added water (1 mL), then extracted with Et$_2$O (3 x 5 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 3:1, R$_f$ = 0.20) to yield 14 mg (65%) of 177 as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.30 (m, 5H), 5.20 (s, 2H), 4.52 (dd, 1H, $J$ = 9.4, 17.8 Hz), 4.57 (dd, 1H, $J$ = 9.1, 18.4 Hz), 3.50 (m, 1H), 2.90 (dd, 1H, $J$ = 7.4, 17.9 Hz), 2.76 (dd, 1H, $J$ = 9.6, 17.9 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.2, 171.1, 135.1, 129.0, 128.8, 128.5, 69.2, 67.8, 40.2, 31.1.
(S)-1-((S)-4-Benzyl-2-oxooxazolidin-3-yl)-2-(hydroxymethyl)pentane-1,4-dione

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A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with methylene chloride (6 mL) and diethyl zinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C and methylene iodide (0.20 mL, 2.5 mmol) was added slowly by syringe. After stirring for 10 minutes, (S)-1-(4-Benzyl-2-oxooxazolidin-3-yl)butane-1,3-dione (0.13 g, 0.5 mmol, in 3 mL of methylene chloride) was added by syringe to the resulting white suspension. The mixture was stirred for 30 minutes. Paraformaldehyde (0.2 g) was added to the solution at one portion. After TLC analysis (hexanes:ethyl acetate = 5:1, Rf = 0.20) indicated the chain extension intermediate was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (2 mL). The solution was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 5:1, Rf = 0.10) to yield 0.11 g (70%) of 181 as a colorless oil with some minor hemiacetal forms. \(^1\)H NMR (400 MHz, CDCl₃) δ 7.33-7.20 (m, 5H), 4.69 (m, 1H), 4.30-4.13 (m, 3H), 3.81 (d, 1H, \(J = 5.9\) Hz), 3.36-3.07 (m, 2H), 2.84-2.71 (m, 2H), 2.36 (d, 1H, \(J = 14.3\) Hz), 2.16 (s, 3H); \(^1\)C NMR (100 MHz, CDCl₃) δ 207.3, 174.3, 154.1, 135.4, 129.7, 129.1, 127.5, 66.7, 63.6, 55.7, 42.7, 41.7, 38.2, 30.0. Hemiacetal: \(^1\)C NMR (100 MHz, CDCl₃) δ 105.9.
3-((tert-Butyldiphenylsilyloxy)methyl)dihydrofuran-2,5-dione 195

A 10-mL round-bottom flask was equipped with a stir bar and charged with THF (4.0 mL), water (1 mL), and compound 191 (71 mg, 0.10 mmol). To this solution was added lithium hydroxide monohydrate (9 mg, 0.2 mmol) and hydrogen peroxide (35 wt. % in water, 0.02 mL, 0.2 mmol). The mixture was allowed to stir for 1 hour at room temperature and extracted with Et₂O (3 x 5 mL). The solution was brought to pH = 1.0 with conc. HCl, then extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo to yield 19 mg (50%) of 195. ¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, 4H, J = 6.4 Hz), 7.42-7.37 (m, 6H), 3.90 (s, 2H), 3.06 (m, 1H), 2.91 (m, 1H), 2.67 (dd, 1H, J = 2.4, 18.3 Hz), 1.04 (s, 9H).

c) Synthesis of a Proposed Inhibitor for Human Cytomegalovirus (HCMV) Protease

Benzyl

(2S,5S)-6-((R)-4-benzyl-2-oxooxazolidin-3-yl)-5-(hydroxymethyl)-3,6-dioxohexan-2-yl(4-methoxybenzyl)carbamate 182

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (4 mL) and diethyl zinc (1.0 M in hexanes, 2.0 mL, 2.0 mmol). The solution was cooled to 0 °C in the ice bath and diiodomethane (0.16 mL, 2.0 mmol) was added dropwise. After
stirring for 10 min, paraformaldehyde (0.5 g, 6 mmol) and benzyl
(S)-5-((R)-4-benzyl-2-oxooxazolidin-3-yl)-3,5-dioxopentan-2-yl(4-methoxybenzyl)carbamate (0.40 mmol, in 0.5 mL of dichloromethane) were added to the resulting white suspension in order. The mixture was stirred for 1 hour. After TLC analysis (hexanes:ethyl acetate = 3:1; \( R_f = 0.20 \)) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (4 mL) and the mixture extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 1:1; \( R_f = 0.20 \)) to yield 0.16 g (68%) of 182 as a colorless oily mixture of two rotamers with a ratio of 1:1. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.38-7.14 (m, 12H), 6.88-6.79 (m, 2H), 5.29-4.89 (m, 2H), 4.69-4.02 (m, 6H), 3.85-3.37 (m, 5H), 3.22 (m, 1H), 2.89-2.03 (m, 5H), 1.26-1.19 (2d, 3H, \( J = 6.9, 6.9 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 201.2, 166.8, 159.4, 159.3, 159.1, 155.8, 153.6, 135.3, 130.1, 129.5, 129.3, 129.0, 128.6, 128.5, 128.2, 127.3, 114.1, 114.0, 67.9, 67.8, 66.3, 62.0, 55.3, 55.1, 51.6, 50.3, 47.4, 42.2, 37.5, 13.9, 13.5, 13.2.

\((R)-4\)-Benzyl-3-((S)-5-oxotetrahydrofuran-3-carbonyl)oxazolidin-2-one 183

A 25-mL round-bottomed flask was equipped with a stir bar and charged with THF (10 mL), water (2.5 mL), and compound 182 (0.35 g, 0.6 mmol). To this solution was
added ceric ammonium nitrate (1.3 g, 2.4 mmol) and the mixture was allowed to stir  
for 30 min at room temperature. The solution was added water (5.0 mL), then  
extracted with Et₂O (3 x 10 mL). The combined organic extracts were dried  
carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was  
chromatographed on silica (hexanes:ethyl acetate = 3:1; R_f = 0.20) yielded 0.13 g  
(75%) of 183 as a viscous colorless oil. ^1H NMR (500 MHz, CDCl₃) δ 7.36-7.17 (m,  
5H), 4.71 (m, 1H), 4.62 (t, 3H, J = 7.9 Hz), 4.42-4.26 (m, 4H), 3.24 (dd, 1H, J = 3.3,  
13.6 Hz), 3.03 (dd, 1H, J = 5.1, 17.7 Hz), 2.88 (dd, 1H, J = 9.1, 13.5 Hz), 2.72 (dd,  
1H, J = 9.1, 17.9 Hz); ^13C NMR (125 MHz, CDCl₃) δ 175.4, 170.7, 153.3, 134.6,  
129.4, 129.1, 127.7, 69.3, 67.0, 55.2, 40.1, 37.8, 30.1.

(5)-5-Oxotetrahydrofuran-3-carboxylic acid 184

A 10-mL round-bottomed flask was equipped with a stir bar and charged with THF  
(4.0 mL), water (1 mL), and compound 183 (62 mg, 0.20 mmol) To this solution was  
added lithium hydroxide monohydrate (17 mg, 0.4 mmol) and hydrogen peroxide (35  
wt. % in water, 0.04 mL, 0.4 mmol). The mixture was allowed to stir for 1 hour under  
room temperature and extracted with Et₂O (3 x 5 mL). The solution was brought to  
pH = 1.0 with conc. HCl, then extracted with ethyl acetate (5 x 5 mL). The combined  
organic extracts were dried carefully over anhydrous sodium sulfate and concentrated  
in vacuo to yield 14 mg (50%) of 184, [α]25^D = -35 (c = 0.002 g/mL, MeOH). ^1H  
NMR (500 MHz, CDCl₃) δ 4.59-4.49 (m, 2H), 3.52 (m, 1H), 2.90 (dd, 1H, J = 7.0,  
208

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17.9 Hz), 2.80 (dd, 1H, $J = 9.7$, 17.9 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.71, 174.66, 68.7, 39.6, 30.7.

$(S)$-Benzyl

2-(3-((($R$)-4-benzyl-2-oxooxazolidin-3-yl)-3-oxopropanoyl)pyrrolidine-1-carboxylate 187

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with $(S)$-1-(benzyloxycarbonyl)pyrrolidine-2-carboxylic acid (125 mg, 0.5 mmol, in 1 mL of tetrahydrofuran), anhydrous tetrahydrofuran (3 mL) and 1,1-carbonyldiimidazole (85 mg, 0.55 mmol) in the indicated order. In a separate 50-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (15 mL) and diisopropylamine (0.28 mL, 2 mmol) in order. After the solution was cooled to 0 °C in the ice bath, $n$-BuLi (2 M in hexanes, 1.0 mL, 2.0 mmol,) was added. After stirring for 10 min, the reaction mixture was cooled to -78 °C, $(R$)-3-acetyl-5-benzyloxazolidin-2-one (0.44 g, 2.0 mmol, in 3 mL of THF) was added over 30 min using a syringe pump. The acyl imidazole solution was transferred to the enolate solution using cannula. After stirring for 30 min, the reaction was quenched by cautious addition of 5 mL 1 M HCl solution. The solution was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed by brine (5
mL). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was chromatographed on silica (hexanes:ethyl acetate = 4:1; *R*<sub>f</sub> = 0.25) to yield 0.20 g (90%) of 187 a colorless oily mixture of two rotamers with a ratio of 1:1. 'H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.37-7.16 (m, 10H), 5.14-5.07 (m, 2H), 4.71 (dd, 1H, *J* = 9.4, 14.3 Hz), 4.40 (m, 1H), 4.32-4.03 (m, 4H), 3.64-3.35 (m, 2H), 2.88-2.75 (m, 2H), 2.28-1.84 (m, 4H); 13C NMR (100 MHz, CDCl<sub>3</sub>) δ 203.5, 203.4, 166.6, 166.4, 155.5, 154.6, 153.9, 153.8, 136.8, 136.5, 135.5, 129.7, 129.5, 129.2, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 127.5, 69.5, 67.7, 67.4, 66.6, 66.3, 65.5, 65.3, 55.3, 54.0, 48.7, 48.0, 47.6, 47.1, 41.7, 37.9, 29.8, 28.7, 24.6, 23.8.

**(S)-Benzyl**

**2-((S)-4-((R)-4-benzyl-2-oxooxazolidin-3-yl)-3-(hydroxymethyl)-4-oxobutanoyl)pyrrolidine-1-carboxylate 188**

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (30 mL) and diethyl zinc (1.0 M in hexanes, 10.0 mL, 10.0 mmol). The solution was cooled to 0 °C in the ice bath and diiodomethane (0.80 mL, 10.0 mmol) was added dropwise. After stirring for 10 min, paraformaldehyde (1.0 g, 11.0 mmol) and compound 187 (0.9 g, 2.0 mmol, in 3 mL of dichloromethane) were added to the resulting white suspension in order. The mixture was stirred for 1 hour. After TLC analysis...
(hexanes:ethyl acetate = 4:1; \( R_f = 0.25 \)) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (10 mL) and the mixture extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine (15 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica to yield 0.78 g (79%) of a colorless oily mixture of rotamaric and hemiacetal forms. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.37-7.19 (m, 10H), 5.16-5.00 (m, 2H), 4.66 (m, 1H), 4.50-4.11 (m, 3H), 4.04-3.45 (m, 5H), 3.25-3.06 (m, 2H), 2.88-2.70 (m, 2H), 2.58-1.84 (m, 5H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 208.3, 208.0, 174.1, 173.9, 173.4, 158.6, 155.2, 154.4, 154.2, 154.1, 153.4, 153.3, 136.8, 136.7, 136.5, 135.6, 135.4, 135.3, 135.2, 129.7, 129.6, 129.3, 129.2, 129.1, 128.8, 128.7, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 109.3, 108.9, 69.9, 69.6, 67.9, 67.6, 67.3, 66.7, 66.6, 66.4, 64.7, 64.4, 64.0, 63.7, 55.7, 55.6, 55.4, 55.3, 48.0, 47.5, 47.0, 44.2, 42.7, 41.6, 41.3, 39.3, 39.0, 38.2, 38.1, 37.9, 30.0, 28.9, 27.8, 27.7, 24.6, 24.5, 23.9.

Benzyl

(2S,5S)-6-((R)-4-benzyl-2-oxazolidin-3-yl)-5-((tert-butyldiphenylsilyloxy)methyl)-3,6-dioxohexan-2-yl(4-methoxybenzyl)carbamate 191

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with \( N,N \)-dimethylformamide.
(10 mL), compound 182 (0.81 g, 1.38 mmol), tert-butylchlorodiphenylsilane (0.73 mL, 2.8 mmol) and imidazole (0.19 g, 2.8 mmol) in the indicated order. After stirring for overnight at room temperature, water (5 mL) was added to the mixture and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried carefully over anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 7:1; Rf = 0.20) to yield 0.89 g (78%) of 191 as a colorless oily mixture of two rotamers with a ratio of 1:1. ¹H NMR (400 MHz, CDCl₃) δ 7.64-7.40 (m, 4H), 7.45-7.39 (m, 7H), 7.28-7.11 (m, 11H), 6.82-6.78 (m, 2H), 5.22-5.02 (m, 2H), 4.65-4.05 (m, 6H), 3.90-3.72 (m, 5H), 3.56-2.25 (m, 5H), 1.24-1.15 (2d, 3H, J = 7.4, 6.4 Hz), 1.04 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 207.1, 207.0, 173.5, 159.2, 159.0, 155.9, 155.8, 153.0, 153.8, 135.6, 133.1, 129.8, 129.7, 129.4, 129.3, 129.0, 128.8, 128.6, 128.5, 128.3, 128.1, 128.0, 127.8, 127.2, 114.0, 67.7, 66.1, 64.2, 61.3, 61.2, 55.2, 51.1, 49.5, 41.4, 41.3, 38.4, 38.2, 38.2, 26.8, 19.3, 13.9, 13.4.

**Benzyl**

**((R)-4-benzyl-2-oxooxazolidin-3-yl)-5-((tert-butyldiphenylsilyloxy)methyl)-3,6-dioxohexan-2-ylcarbamate 192**

A 50-mL round-bottom flask was equipped with a stir bar and charged with THF (20 mL), water (5 mL), and compound 191 (1.48 g, 1.8 mmol). CAN (4.0 g, 7.2 mmol) was added to this solution in one portion and the mixture was allowed to stir for 30
min at room temperature. The solution was added by water (5 mL) and extracted with
diethyl ether (3 x 10 mL). The combined organic layers were dried carefully over
anhydrous sodium sulfate and concentrated in vacuo. The residue was
chromatographed on silica (hexanes:ethyl acetate = 3:1; Rf = 0.20) to yield 1.1 g (87%)
of 192 as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.65 (d, 4H, J = 6.9 Hz),
7.43-7.22 (m, 14H), 7.14 (d, 2H, J = 7.0 Hz), 5.47 (d, 1H, NH, J = 6.9 Hz), 5.08 (s,
2H), 4.68 (m, 1H), 4.42-4.34 (m, 2H), 4.20 (dd, 1H, J = 8.4, 8.8 Hz), 4.10 (dd, 1H, J =
2.9, 9.1 Hz), 3.98 (dd, 1H, J = 5.2, 10.1 Hz), 3.90 (dd, 1H, J = 4.9, 10.0 Hz), 3.34 (dd,
1H, J = 10.8, 18.4 Hz), 3.24 (dd, 1H, J = 3.1, 13.4 Hz), 2.61-2.51 (m, 2H), 1.40 (d, 3H,
J = 7.1 Hz), 1.06 (s, 9H); ¹³C NMR (500 MHz, CDCl₃) δ 207.6, 173.0, 155.6, 153.2,
135.7, 135.6, 135.4, 133.1, 133.0, 130.0, 129.4, 129.0, 128.9, 128.6, 128.2, 128.1,
127.9, 127.3, 66.9, 66.2, 64.2, 55.3, 55.2, 41.2, 38.2, 26.8, 19.4, 18.0.

(5S,8S)-5,12,12-Trimethyl-3,6-dioxo-1,11,11-triphenyl-2,10-dioxa-4-aza-11-silatri
decane-8-carboxylic acid 197

A 10-mL oven-dried, round-bottomed flask equipped with a stir bar was charged with
tetrahydrofuran (2 mL), compound 192 (70 mg, 0.10 mmol, in 0.5 mL of THF) in the
indicated order. Lithium hydroxide monohydrate (5.0 mg, 0.11 mmol, in 2 mL of
deionized water) was added in 10 min using syringe pump. The solution was stirred
till TLC analysis (hexanes:ethyl acetate = 3:1; Rf = 0.20) indicated that the starting
material was consumed. The mixture was acidified to pH = 1 using 1 M HCl, then
extracted with ethyl acetate (3 x 2 mL). The combined organic layers were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 1:1; R_f = 0.20) to yield 40 mg (70%) of 197 as a colorless oil. ^1 H NMR (400 MHz, MeOD) δ 7.64 (d, 4H, J = 6.3 Hz), 7.44-7.23 (m, 11H), 5.06 (s, 2H), 4.90 (s, 1H), 4.24 (m, 1H), 3.96 (dd, 1H, J = 4.9, 9.6 Hz), 3.77 (dd, 1H, J = 3.6, 8.8 Hz), 3.17 (dd, 1H, J = 8.9, 17.9 Hz), 3.04 (dd, 1H, J = 4.2, 18.6 Hz), 2.77 (dd, 1H, J = 3.7, 17.9 Hz), 1.29 (d, 3H, J = 7.2 Hz), 1.02 (s, 9H); ^13 C NMR (100 MHz, CDC13 ) δ 208.9, 175.4, 157.1, 137.0, 135.5, 133.2, 133.1, 129.8, 128.3, 127.8, 127.7, 127.6, 66.5, 64.4, 55.7, 43.0, 37.5, 26.1, 19.0, 15.4.

(5)-Methyl 2-((2R,5S)-5-(benzoxycarbonylamino)-2-((tert-butyldiphenylsilyloxy)methyl)-4-oxohexanamido)propanoate 198

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with N,N-dimethylformamide (3 mL), compound 197 (0.27 g, 0.5 mmol), EDC (0.20 g, 1.0 mmol), HOBt (0.15 g, 1.0 mmol), alanine methyl ester hydrochloride (0.15 g, 1.0 mmol) and sodium bicarbonate (0.08 g, 1.0 mmol) were added in the indicated order. The reaction was stirred at room temperature for overnight and diethyl ether (5 mL) was added to the solution. The organic phase was washed with 1M HCl (2 x 3 mL), brine (3 mL), sat.
NaHCO₃ (2 x 3 mL) and brine (3 mL) in the indicated order. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 5:1; Rₛ = 0.30) to yield 0.23 g (73%) of 198 as colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.64 (d, 4H, J = 7.8 Hz), 7.45-7.26 (m, 11H), 6.84 (d, 1H, -NH, J = 7.5 Hz), 5.45 (d, 1H, -NH, J = 6.8 Hz), 5.08 (d, 2H, 1H, J = 2.0 Hz), 4.55 (q, 1H, J = 7.2 Hz), 4.31 (q, 1H, J = 7.1 Hz), 3.85 (dd, 1H, J = 10.1, 10.1 Hz), 3.70 (s, 3H), 3.64 (dd, 1H, J = 4.8, 9.9 Hz), 3.05-2.95 (m, 2H), 2.42 (dd, 1H, J = 3.0, 16.9 Hz), 1.38 (d, 3H, J = 7.2 Hz), 1.35 (d, 3H, J = 7.2 Hz), 1.05 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 207.4, 173.3, 172.4, 155.8, 135.8, 132.9, 130.2, 128.7, 128.4, 128.3, 128.1, 67.0, 64.7, 55.7, 52.5, 48.3, 43.8, 37.9, 27.0, 19.3, 18.5, 18.0.

(2S)-Methyl 2-((5S)-2-((tert-butyldiphenylsilyloxy)methyl)-4-oxo-5-(tosyloxyamino)hexanamido)propanoate 199

A 25-mL oven-dried, two-necked round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with 2-propanol (6 mL), compound 198 (0.25 g, 0.40 mmol, in 0.5 mL of THF), anhydrous p-toluenesulfonic acid (69 mg, 0.40 mmol) and 10 % Pd on carbon (15 mg) in the indicated order. The vessel was purged with hydrogen and the nitrogen was removed. The suspension was allowed to stir at room temperature for overnight. The suspension was filtered and concentrated in vacuo to yield 0.24 g (90%) of 199 as a colorless oil.
\(^1\)H NMR (400 MHz, MeOD) \(\delta\) 7.72-7.22 (m, 14H), 4.40 (q, 1H, \(J = 7.3\) Hz), 4.12 (q, 1H, \(J = 7.4\) Hz), 3.86 (dd, 1H, \(J = 6.2, 9.8\) Hz), 3.74 (dd, 1H, \(J = 5.7, 15.6\) Hz), 3.62 (s, 3H), 3.18-3.06 (m, 2H), 2.58 (dd, 1H, \(J = 3.1, 17.5\) Hz), 2.34 (s, 3H), 1.48 (d, 3H, \(J = 7.3\) Hz), 1.36 (d, 3H, \(J = 7.2\) Hz), 1.04 (s, 9H); \(^1^3\)C NMR (100 MHz, MeOD) \(\delta\) 204.6, 173.4, 173.1, 140.5, 135.6, 133.1, 129.9, 128.7, 128.3, 127.8, 127.6, 125.8, 64.9, 63.6, 54.5, 51.6, 43.7, 37.1, 26.2, 24.2, 20.3, 19.0, 16.7, 14.8.

(2S)-methyl

2-((3S)-5-((5S)-1-(benzyloxy carbonylamino)ethyl)-5-hydroxytetrahydrofuran-3-carboxamido)propanoate 199A

A 5-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with THF (2 mL) and compound 198 (32 mg, 0.05 mmol, in 0.5 mL of THF) in order. After the solution was cooled to 0 °C in the ice bath, TBAF (1 M in THF, 0.10 mL, 0.10 mmol) was added. After TLC analysis (hexanes:ethyl acetate = 5:1; \(R_f = 0.30\)) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (2 mL). The mixture was extracted with ethyl acetate (2 x 5 mL). The combined organic layers were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 1:1, \(R_f = 0.10\)) to offer 15 mg (76%) of 199A as a colorless
liquid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38-7.29 (m, 5H), 6.59 (d, 1H, $J = 7.3$ Hz), 5.17-5.03 (m, 3H), 4.55 (q, 1H, $J = 7.3$ Hz), 4.14 (m, 2H), 4.00-3.55 (m, 2H), 3.75 (s, 3H), 3.02 (m, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 1.42 (d, 3H, $J = 7.2$ Hz), 1.28 (d, 3H, $J = 7.7$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.0, 173.3, 156.2, 156.0, 136.8, 128.7, 128.3, 107.0, 71.2, 66.9, 53.6, 53.0, 52.9, 51.5, 48.8, 48.7, 44.4, 43.5, 40.1, 18.4, 15.8.

(6S,9S,12S,15S)-Methyl

12-((tert-butylidiphenylsilyloxy)methyl)-6-(2-(dimethylamino)-2-oxoethyl)-2,2,9,15-tetramethyl-4,7,10,13-tetraoxo-3-oxa-5,8,14-triazahexadecan-16-oate 200

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with compound 199 (0.27 g, 0.5 mmol), N,N-dimethylformide (3 mL), EDC (0.20 g, 1.0 mmol), HOBt (0.15 g, 1.0 mmol), compound 144 (0.15 g, 1.0 mmol) and sodium bicarbonate (0.08 g, 1.0 mmol) were added in the indicated order. The reaction was stirred at room temperature for overnight and diethyl ether (5 mL) was added to the solution. The organic phase was washed with 1M HCl (2 x 3 mL), brine (3 mL), sat. NaHCO$_3$ (2 x 3 mL) and brine (3 mL) in the indicated order. The resulting liquid was filtered and concentrated under reduced pressure. The residue was chromatographed on silica (ethyl acetate; $R_f = 0.10$) to yield 0.23 g (73%) of 200 as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.65-7.64 (d, 4H, $J = 7.8$ Hz), 7.46-7.37 (m, 6H), 6.85 (d, 1H, -NH, $J = 7.5$ Hz), 6.08 (d, 1H, -NH, $J = 7.9$ Hz), 4.58-4.38 (m, 3H), 3.84 (dd, 1H, $J = 8.4, 10.1$ Hz), 3.70 (s,
3H), 3.63 (dd, 1H, $J = 5.3, 10.1$ Hz), 3.16-2.85 (m, 3H), 2.97 (s, 3H), 2.87 (s, 3H),
2.53 (dd, 1H, $J = 7.6, 18.1$ Hz), 2.40 (dd, 1H, $J = 3.9, 17.4$ Hz), 1.45 (s, 9H), 1.37 (d,
3H, $J = 7.2$ Hz), 1.32 (d, 3H, $J = 7.2$ Hz), 1.05 (s, 9H); $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$
207.1, 173.3, 172.5, 171.4, 171.2, 155.8, 143.5, 135.7, 133.0, 130.1, 128.7, 128.4, 128.4,
128.3, 128.1, 127.9, 80.3, 64.8, 54.5, 52.5, 50.9, 48.3, 43.8, 37.9, 37.4, 35.5, 29.9,
28.5, 27.0, 19.3, 18.5, 17.1.

(2S)-methyl

2-((3S)-5-(((S)-1-((S)-2-(tert-butoxycarbonylamino)-4-(dimethylamino)-4-oxobutanamido)ethyl)-5-hydroxytetrahydrofuran-3-carboxamido)propanoate 202

A 5-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of
nitrogen through a needle and a stir bar, was charged with THF (2 mL) and compound
200 (20 mg, 0.026 mmol) in order. After the solution was cooled to 0 °C in the ice
bath, tetrabutylammonium fluoride (1 M in THF, 0.05 mL, 0.05 mmol) was added.
After TLC analysis (ethyl acetate; $R_f = 0.10$) indicated that the starting material was
consumed, the solution was quenched by cautious addition of saturated aqueous
ammonium chloride (1 mL). The mixture was extracted with ethyl acetate (3 x 5 mL).
The combined organic layers were washed with brine (2 mL) and dried over
anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under
reduced pressure. The product was purified by flash chromatography on silica (ethyl
acetate:methanol = 5:1, $R_f = 0.10$) to offer 5 mg (38%) of 202. $^1$H NMR (500 MHz,
CDCl$_3$ $\delta$ 6.83 (d, 1H, $J = 9.8$ Hz), 6.49 (d, 1H, $J = 7.2$ Hz), 6.30 (s, 1H), 6.17 (d, 1H, $J = 8.3$ Hz), 5.26 (d, 1H, $J = 8.3$ Hz), 5.04 (d, 1H, $J = 3.7$ Hz), 4.54 (dd, 1H, $J = 7.2$ Hz), 4.42 (m, 1H), 4.18-4.11 (m, 2H), 3.77-3.73 (m, 4H), 3.22-2.90 (m, 8H), 2.65-2.54 (m, 2H), 2.15 (m, 1H), 1.60-1.22 (m, 15H).

d) Formal Synthesis of (+)-Brefeldin A

$(2E,6S,10E,11aS,13S,14aR)-13$-(Methoxymethoxy)-6-methyl-6,7,8,9,12,13,14,14a-octahydro-1H-cyclopenta[f][1]oxacyclotridecine-1,4(11aH)-dione 260

A 10-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 3 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 0.5 mL, 0.5 mmol). The solution was cooled to 0 °C and compound 294A (25 mg, 0.08 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, methylene iodide (0.02 mL, 0.5 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 hour at room temperature. Diethyl zinc (1.0 M in hexanes, 0.25 mL, 0.25 mmol) was added to the solution at room temperature and after 10 minutes, methylene iodide (0.02 mL, 0.25 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 hour at room temperature. Iodine (0.5 g, 2.0 mmol) was added to the reaction mixture in a single portion and allowed to stir until a pink color persisted for 30 seconds. A saturated solution of sodium thiosulfate (2 mL) was added and the mixture was stirred until the pink color had disappeared. To this solution was added DBU.
(0.15 mL, 1.0 mmol) and the mixture was stirred for 1 minute, washed with saturated aqueous ammonium chloride (5 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate =7:1; R_f = 0.25) to yield 12 mg (46%) of 260 as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 7.76 (d, 1H, J = 16.0 Hz), 6.44 (d, 1H, J = 15.8 Hz), 5.86 (ddd, 1H, J = 4.1, 10.9, 15.1 Hz), 5.52 (ddd, 1H, J = 1.3, 9.6, 15.2 Hz), 4.56 (m, 1H), 4.63 (s, 2H), 4.10 (m, 1H), 3.36 (s, 3H), 2.88 (q, 1H, J = 9.1 Hz), 2.56 (q, 1H, J = 9.1 Hz), 2.30-2.21 (m, 2H), 2.14 (m, 1H), 2.02 (m, 1H), 1.96-1.88 (m, 2H), 1.80 (m, 1H), 1.68-1.58 (m, 2H), 1.33 (d, 3H, J = 6.1 Hz), 1.22 (m, 1H); ^13C NMR (125 MHz, CDCl_3) δ 200.5, 166.1, 140.2, 135.7, 132.9, 128.3, 95.2, 77.2, 73.7, 56.0, 55.3, 45.2, 40.3, 34.2, 32.7, 32.2, 25.6, 20.2.

(10aS,13aR,E)-5,6,7,8,11,12,13,13a-Octahydrocyclopenta[e][1]oxacyclododecine-1,3(2H,10aH)-dione 262A

Procedure 1:

A 250-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (100 mL), compound 263 (0.16 g, 0.6 mmol, in 1 mL of dichloromethane) and bis(cyclohexylphosphine)benzylidine ruthenium (IV) dichloride (20 mg, 0.024 mmol) in the indicated order. This solution was heated to reflux for 8 hours and another
portion of catalyst was added (20 mg, 0.024 mmol). Reflux was continued for an additional 8 hours till TLC analysis (hexanes:ethyl acetate = 15:1, \( R_f = 0.20 \)) indicated that the starting material was consumed. The solution was allowed to cool and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 10:1, \( R_f = 0.20 \)) to yield 100 mg (70 %) of two isomers 262A (55%) and 262B (15%). The compounds were produced in \( E:Z = 3.5:1 \) ratio (based on \(^1\)H NMR of the crude reaction mixture ). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.41 (ddd, 1H, \( J = 5.0, 9.8, 15.0 \) Hz), 5.26 (dd, 1H, \( J = 8.9, 16.6 \) Hz), 4.42 (m, 1H), 3.82 (m, 1H), 3.41 (s, 2H), 3.02 (dd, 1H, \( J = 8.7, 18.7 \) Hz), 2.64 (m, 1H), 2.16 (m, 1H), 1.94-1.56 (m, 9H), 1.44-1.32 (m, 2H); \(^1\)C (100 MHz, CDCl\(_3\)) \( \delta \) 205.7, 167.5, 133.1, 131.9, 65.8, 57.3, 50.9, 48.7, 33.8, 31.6, 29.7, 26.7, 25.1, 24.7.

(10aS,13aR,Z)-5,6,7,8,ll,12,13,13a-Octahydrocyclopenta[e][1]oxacyclododecine-1,3(2H,10aH)-dione 262B (hexanes:ethyl acetate = 7:1, \( R_f = 0.20 \))

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.34 (dd, 1H, \( J = 9.9, 9.9 \) Hz), 5.22 (dd, 1H, \( J = 10.9, 10.9 \) Hz), 4.54 (m, 1H), 3.84 (m, 1H), 3.52 (d, 1H, \( J = 14.3 \) Hz), 3.38 (d, 1H, \( J = 14.3 \) Hz), 3.18 (m, 1H), 2.50 (m, 1H), 2.42 (m, 1H), 2.03-1.53 (m, 8H), 1.45-1.38 (m, 1H); \(^1\)C (100 MHz, CDCl\(_3\)) \( \delta \) 205.6, 166.8, 133.5, 130.4, 67.4, 60.1, 47.2, 41.8, 34.5, 29.5, 28.0, 26.1, 25.4, 25.3.

**Procedure 2:**

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with toluene (4 mL). Compound
262B (10 mg, 0.04 mmol), thiophenol (0.014 mL, 0.14 mmol) and AIBN (10 mg, 0.06 mmol) were added sequentially to the flask. The solution was heated to 80 °C for 8 hours. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexanes:ethyl acetate = 10:1, Rf = 0.20) to give 6 mg (60%, based on 75% conversion) of 262A.

Hex-5-enyl 3-oxo-3-((1R,2S)-2-vinylcyclopentyl)propanoate 263

A 5-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with anhydrous THF (2 mL), compound 264 (0.14 g, 1.0 mmol, in 1 mL of THF), and 1,1-carbonyldiimidazole (0.17 g, 1.1 mmol) in the indicated order. A separate 50-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (10 mL), and diisopropylamine (0.56 mL, 4 mmol) in order. After the solution was cooled to 0 °C in the ice bath, n-BuLi (2.0 M in hexanes, 2.0 mL, 4.0 mmol) was added dropwise. After stirring for 10 min, the reaction mixture was cooled to -78 °C, compound 283 (0.56 g, 4 mmol, in 5 mL of THF) was added in 1 h using a syringe pump. The acyl imidazole solution was transferred to the enolate solution by cannula. After stirring for 30 min, the reaction was quenched by cautious addition of 1 M HCl (5 mL). The solution was extracted with diethyl ether (3 x 10 mL) and the combined organic layer was washed by brine (15 mL). The organic layers were dried over anhydrous sodium sulfate,
filtered and concentrated *in vacuo*. The residue was chromatographed on silica (hexanes:ethyl acetate = 15:1, *R* = 0.20) to yield 0.21 g (80%) of 263 as a colorless liquid with some minor enol forms present. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.84-5.71 (m, 2H), 5.08-4.95 (m, 4H), 4.14-4.11 (m, 2H), 3.47 (s, 2H), 2.80 (m, 1H), 2.70 (m, 1H), 2.10-2.05 (m, 2H), 1.96-1.86 (m, 2H), 1.74-1.62 (m, 4H), 1.51-1.41 (m, 4H); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 203.5, 166.5, 140.0, 113.8, 113.8, 64.2, 56.5, 48.2, 46.7, 32.4, 32.2, 27.9, 26.9, 24.0, 23.8. Resonances observed for the enol forms: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.1 (s, 1H).

**(1R,2S)-2-Vinylcyclopentanecarboxylic acid 264**

Compound 274 (0.25 g, 1.5 mmol) was dissolved in a 25-mL round-bottomed flask with 3 mL of THF. Water (3 mL) and lithium hydroxide monohydrate (0.27 g, 6.0 mmol) were added to the solution in the indicated order. The mixture was allowed to stir overnight at room temperature and the solution was brought to pH = 1.0 with 1M HCl, then extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried carefully over anhydrous sodium sulfate and concentrated *in vacuo* to yield 0.18 g (85%) of 264 as a colorless liquid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.80 (m, 1H), 5.08 (dd, 1H, $J = 1.2, 17.1$ Hz), 4.99 (d, 1H, $J = 10.3$ Hz), 2.76 (m, 1H), 2.54 (dd, 1H, $J = 8.7, 17.4$ Hz), 2.06-1.88 (m, 3H), 1.74 (m, 2H), 1.46 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.2, 137.3, 113.8, 63.4, 32.3, 27.0, 24.2, 19.9.

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(1R,2S)-Ethyl 2-vinylcyclopentanecarboxylate 272

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (2 mL) and compound 280 (0.19 g, 0.5 mmol, in 0.5 mL of tetrahydrofuran) in order. After the solution was cooled to 0 °C in the ice bath, TBAF (1.0 mL, 1.0 mmol, 1.0 M in tetrahydrofuran) was added in one portion. After TLC analysis (hexanes:ethyl acetate = 7:1, Rf = 0.25) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (1 mL). The mixture was extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 15:1, Rf = 0.30) to offer 76 mg (90%) of 272 as a colorless liquid. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.78 (m, 1H), 5.04 (d, 1H, J = 17.1 Hz), 4.95 (d, 1H, J = 10.2 Hz), 4.18-4.08 (m, 2H), 2.73 (m, 1H), 2.56 (m, 1H), 2.01-1.83 (m, 3H), 1.75-1.65 (m, 2H), 1.42 (m, 1H), 1.24 (t, 3H, J = 7.1 Hz).

(1R,2R)-Ethyl

2-((1R)-1-(p-tolylsulfinyl)-2-(trimethylsilyl)ethyl)cyclopentanecarboxylate 280

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (6 mL),
and diisopropyl amine (0.2 mL, 1.5 mmol) in order. After the solution was cooled to 0 °C, \( n \)-BuLi (2.0 M in hexanes, 0.75 mL, 1.5 mmol) was added in one portion. After stirring for 10 min, the reaction mixture was cooled to -78 °C using dry ice in acetone, compound 276 (0.12 g, 0.50 mmol, in 0.5 mL of THF) was added. After the solution was allowed to stir for 15 min, compound 279 (0.22 g, 1.0 mmol, in 1 mL of THF) was added in one portion. The solution was allowed to stir for 15 min at -78 °C and then warm to 0 °C. After TLC analysis (hexanes:ethyl acetate = 3:1; \( R_f = 0.20 \)) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (3 x 10 mL), washed with brine (10 mL). The combined organic layers were dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1, \( R_f = 0.25 \)) to offer 0.15 g (78%) of 280 as a colorless liquid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.56 (d, 2H, \( J = 8.3 \) Hz), 7.47 (d, 2H, \( J = 8.3 \) Hz), 4.36 (q, 2H, \( J = 7.1 \) Hz), 3.35 (dd, 1H, \( J = 8.6, 18.6 \) Hz), 3.00 (ddd, 1H, \( J = 2.7, 2.7, 11.7 \) Hz), 2.67 (m, 1H), 2.58 (s, 3H), 2.30-1.87 (m, 6H), 1.48 (t, 3H, \( J = 7.1 \) Hz), 1.03 (dd, 1H, \( J = 11.7, 15.1 \) Hz), 0.92 (dd, 1H, \( J = 2.7, 15.0 \) Hz), 0.00 (s, 9H); \(^1^3\)C (125 MHz, CDCl\(_3\)) \( \delta \) 176.8, 141.7, 131.0, 129.9, 125.4, 67.3, 62.0, 49.4, 49.2, 30.8, 28.9, 25.8, 22.7, 15.8, 10.6, 0.0.
Procedure 1:

A 250-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (100 mL), compound 285 (169 mg, 0.5 mmol, in 1 mL of dichloromethane) and bis(cyclohexylphosphine)benzylidine ruthenium (IV) dichloride (20 mg, 0.024 mmol) in the indicated order. This solution was heated to reflux for 8 hours and another portion of catalyst was added (20 mg, 0.024 mmol). Reflux was continued for an additional 8 hours till TLC analysis (hexanes:ethyl acetate =10:1; Rf = 0.20) indicated that the starting material was consumed. The solution was allowed to cool and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate =10:1; Rf = 0.15) to yield 100 mg (64%) of 284A (50%) and 284B (14%) as a mixture of two isomers existing in E:Z = 3.6:1 ratio (based on 1H NMR of crude reaction mixture). 284A : 1H NMR (500 MHz, CDCl3) δ 5.38 (m, 1H), 5.30 (dd, 1H, J = 8.5, 16.2 Hz), 5.04 (m,1H), 4.61 (s, 2H), 4.15 (m, 1H), 3.44 (m, 1H), 3.40-3.38 (m, 2H), 3.36 (s, 3H), 2.59 (m, 1H), 2.26-2.15 (m, 2H), 2.04-1.92 (m, 2H), 1.72-1.52 (m, 5H), 1.33 (m, 1H), 1.19 (d, 3H, J = 6.5 Hz); 13C NMR (125 MHz, CDCl3) δ 205.4, 167.3, 133.6, 131.7, 95.4, 77.4, 71.6, 55.6, 53.9, 50.8, 46.0, 40.3, 36.0, 32.0, 31.6, 20.7, 18.5.
(5S,9aS,11S,12aR,Z)-11-(Methoxymethoxy)-5-methyl-5,6,7,9a,10,11,12,12a-octahydro-1H-cyclopenta[e][1]oxacycloundecine-1,3(2H)-dione

284B (hexanes:ethyl acetate =7:1; Rf = 0.15)

1H NMR (500 MHz, CDCl3) δ 5.42 (ddd, 1H, J = 1.4, 5.4, 5.4 Hz), 5.30 (ddd, 1H, J = 1.4, 5.4, 5.4 Hz), 5.05 (m, 1H), 4.62 (s, 2H), 4.24 (m, 1H), 3.50 (d, 1H, J = 14.0 Hz), 3.38 (d, 1H, J = 14.2 Hz), 3.35 (s, 3H), 3.16 (m, 1H), 2.98 (dd, 1H, J = 8.2, 16.4 Hz), 2.37-2.22 (m, 2H), 2.04-1.74 (m, 5H), 1.58-1.43 (m, 3H), 1.23 (d, 3H, J = 6.4 Hz);

13C NMR (125 MHz, CDCl3) δ 203.8, 165.0, 132.1, 129.8, 94.4, 76.6, 72.0, 56.4, 54.4, 47.8, 39.3, 38.8, 35.2, 30.7, 25.8, 22.9, 17.8.

Procedure 2:

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with toluene (4 mL). Compound 284B (10 mg, 0.03 mmol), thiophenol (0.014 mL, 0.14 mmol) and AIBN (10 mg, 0.06 mmol) were added sequentially to the flask. The solution was heated to 80 °C for 8 hours. The mixture was concentrated in vacuo, and the resulting residue was purified by column chromatography on silica gel (hexanes:ethyl acetate =10:1; Rf = 0.15) to give 5 mg (50%, based on 78% conversion) of 284A.
(S)-Hept-6-en-2-yl

3-((1R,2S,4S)-4-(methoxymethoxy)-2-vinylcyclopentyl)-3-oxopropanoate 285

A 5-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with anhydrous THF (2 mL), compound 286 (0.10 g, 0.5 mmol, in 1 mL of THF), and 1,1-dicarbonylimidazole (0.10 g, 0.6 mmol) in the indicated order. In a separate 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (8 mL), and diisopropyl amine (0.28 mL, 2 mmol) in order. After the solution was cooled to 0 °C in the ice bath, n-BuLi (2.0 M in hexanes, 1.0 mL, 2.0 mmol) was added dropwise. After stirring for 10 min, the reaction mixture was cooled to -78 °C, compound 313 (0.31 g, 2 mmol, in 3 mL of THF) was added in 1 hour using syringe pump. The acyl imidazole solution was transferred to the enolate solution by cannula. After stirring for 30 min, the reaction was quenched by cautious addition of 1 M HCl (2 mL). The solution was extracted with diethyl ether (3 x 5 mL) and the combined organic layers were washed by brine (5 mL). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was chromatographed on silica (hexanes:ethyl acetate = 10:1, Rf = 0.20) to yield 0.14 g (85%) of 285 as a colorless liquid. 1H NMR (500 MHz, CDCl3) δ 5.87-5.74 (m, 2H), 5.08-4.93 (m, 4H), 4.62 (s, 2H), 4.17 (m, 1H), 3.44 (s, 2H), 3.35 (s, 3H), 3.04 (dd, 1H, J = 8.9, 17.6 Hz), 2.70 (m, 1H), 2.26 (m, 1H), 2.11-1.96 (m, 4H), 1.64-1.35 (m, 6H), 1.23 (d, 3H, J = 6.3 Hz);
(1R,2S,4S)-4-(Methoxymethoxy)-2-vinylcyclopentanecarboxylic acid 286

Compound 309 (0.46 g, 2.0 mmol) was dissolved in a 25-mL round-bottomed flask with 4 mL of THF. Water (4 mL), and lithium hydroxide monohydrate (0.38 g, 8.0 mmol) were added to the solution in the indicated order. The mixture was allowed to stir for overnight at room temperature and the solution was brought to pH = 1.0 with 1M HCl, then extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried carefully over anhydrous sodium sulfate and concentrated in vacuo to yield 0.32 g (80%) of 286 as a colorless liquid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.85 (m, 1H), 5.09 (d, 1H, $J =$ 7.2 Hz), 5.01 (d, 1H, $J =$ 10.2 Hz), 4.63 (s, 2H), 4.25 (m, 1H), 3.36 (s, 3H), 2.78-2.76 (m, 2H), 2.32 (m, 1H), 2.12-2.10 (m, 2H), 1.62 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 180.5, 140.4, 115.1, 95.5, 55.6, 48.2, 46.3, 39.7, 37.2.

(S,E)-Ethyl 6-bromo-5-(methoxymethoxy)hex-2-enoate 294

Procedure 1:

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (40 mL), compound 303 (2.12 g, 9.0 mmol, in 4.5 mL of dichloromethane), and MOM-Cl (1.0 mL, 13.5 mmol) in the indicated order. After the solution was cooled to 0 °C in the ice
bath, diisopropylethylamine (2.4 mL, 13.5 mmol) was added in one portion. After overnight reaction at room temperature, diethyl ether (25 mL) was added to the mixture and the solution was washed with 1M HCl (3 x 10 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1, Rf = 0.25) to offer 2.0 g (79%) of 294 as a colorless liquid. 1H NMR (400 MHz, CDCl3) δ 6.93 (m, 1H), 5.95 (d, 1H, J = 15.6 Hz), 4.75-4.68 (m, 2H), 4.22-4.17 (m, 2H), 3.89 (m, 1H), 3.46 (d, 2H, J = 5.5 Hz), 3.41 (s, 3H), 2.63-2.58 (m, 2H), 1.29 (t, 3H, J = 7.1 Hz); 13C NMR (100 MHz, CDCl3) δ 166.1, 143.3, 124.6, 96.1, 75.4, 60.3, 56.0, 36.0, 34.6, 14.2.

Procedure 2:

Compound 302 (74 mg, 0.2 mmol) was dissolved in a 5-mL round-bottomed flask with 2 mL of THF. Sodium bromide (0.1 g, 1.0 mmol) was added to the solution and the mixture was allowed to stir for overnight under room temperature and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried carefully over anhydrous sodium sulfate and concentrated in vacuo to yield 44 mg (79%) 294 of as a colorless liquid.

(R,E)-Ethyl 5-(methoxymethoxy)-6-(tosyloxy)hex-2-enoate 302

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (3 mL),
compound 301 (82 mg, 0.25 mmol, in 0.5 mL of dichloromethane), and MOM-Cl (0.05 mL, 0.68 mmol) in the indicated order. After the solution was cooled to 0 °C in the ice bath, Diisopropylethylamine (0.18 mL, 1.0 mmol,) was added in one portion. After overnight reaction at room temperature, diethyl ether (25 mL) was added to the mixture and the solution was washed with 1M HCl (3 x 5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1, Rf = 0.30) to offer 60 mg (65%) of 302 as a colorless liquid.  

**1H NMR (500 MHz, CDCl3)** δ 7.79 (d, 2H, J = 8.1 Hz), 7.36 (d, 2H, J = 8.1 Hz), 6.83 (m, 1H), 5.84 (d, 1H, J = 16.8 Hz), 4.62 (d, 1H, J = 7.1 Hz), 4.57 (d, 1H, J = 7.1 Hz), 4.17 (q, 2H, J = 7.1 Hz), 4.02-4.01 (m, 2H), 3.87 (m, 1H), 3.31 (s, 3H), 2.46 (s, 3H), 2.46-2.42 (m, 2H), 1.28 (q, 3H, J = 7.2 Hz); **13C (125 MHz, CDCl3)** δ 166.0, 145.1, 142.9, 132.7, 129.9, 128.0, 124.6, 96.1, 73.5, 70.5, 60.4, 55.8, 34.4, 21.7, 14.3.

**(S,E)-Ethyl 6-bromo-5-hydroxyhex-2-enoate 303**

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with dichloromethane (30 mL), compound 300 (0.87 g, 5.0 mmol, in 5 mL of dichloromethane), and carbon tetrabromide (2.0 g, 6.0 mmol) in the indicated order. After the solution was cooled to 0 °C in the ice bath, triphenylphosphine (1.6 g, 6.0 mmol, in 5 mL of dichloromethane) was added in 30 minutes using syringe pump. After TLC analysis (hexanes:ethyl
acetate = 1:1; \( R_f = 0.15 \) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (15 mL). The mixture was extracted with diethyl ether (2 x 15 mL). The combined organic layers was washed with brine (10 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 3:1, \( R_f = 0.30 \)) to offer 0.83 g (70%) of 303 as a colorless liquid. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 6.95 (m, 1H), 5.94 (d, 1H, \( J = 16.6 \) Hz), 4.20 (q, 2H, \( J = 7.2 \) Hz), 3.98 (m, 1H), 3.64 (dd, 1H, \( J = 3.9, 11.3 \) Hz), 3.52 (dd, 1H, \( J = 6.5, 11.2 \) Hz), 2.53-2.48 (m, 2H), 2.36 (m, 1H, OH), 1.29 (t, 3H, \( J = 7.2 \) Hz); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 166.2, 143.3, 124.5, 69.7, 60.5, 39.0, 37.8, 14.2.

\((4R)-\text{Ethyl} \)

4-(methoxymethoxy)-2-(1-(p-tolylsulfinyl)-2-(trimethylsilyl)ethyl)cyclopentane carboxylate 304

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (3 mL), and diisopropylamine (0.1 mL, 0.75 mmol) in order. After the solution was cooled to 0 \(^\circ\)C, \( n \)-BuLi (2.0 M in hexanes, 0.37 mL, 0.75 mmol) was added in one portion. After stirring for 10 min, the reaction mixture was cooled to -78 \(^\circ\)C using dry ice in acetone, compound 276 (0.07 g, 0.30 mmol, in 0.5 mL of THF) was added. After the solution
was allowed to stir for 15 min, 294 (0.12 g, 0.45 mmol, in 0.33 mL of THF) was added in one portion. The solution was allowed to stir for 15 min at -78 °C and then warm to 0 °C. After TLC analysis (hexanes:ethyl acetate = 3:1; R<sub>f</sub> = 0.20) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (2 mL). The mixture was extracted with diethyl ether (3 x 5 mL), washed with brine (5 mL). The combined organic layers were dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexane: ethyl acetate = 4:1; R<sub>f</sub> = 0.30) to offer 95 mg (72%) of 304 as a colorless liquid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.57 (d, 2H, <i>J</i> = 8.2 Hz), 7.50 (d, 2H, <i>J</i> = 8.2 Hz), 4.82 (s, 2H), 4.48 (m, 1H), 4.44-4.37 (m, 2H), 3.56 (d, 1H, <i>J</i> = 11.8 Hz), 3.55 (s, 3H), 3.44 (m, 1H), 3.10-3.03 (m, 2H), 2.60 (s, 3H), 2.43-2.30 (m, 2H), 2.22 (m, 1H), 1.50 (t, 3H, <i>J</i> = 12 Hz), 1.06 (dd, 1H, <i>J</i> = 11.7, 15.0 Hz), 0.90 (dd, 1H, <i>J</i> = 2.5, 15.0 Hz), 0.05 (s, 9H); <sup>1</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.8, 141.8, 141.3, 131.0, 125.4, 96.3, 77.3, 66.7, 62.2, 56.7, 47.5, 46.3, 37.1, 35.8, 22.7, 15.7, 10.4, 1.4.

**(<i>4S</i>)-Ethyl 4-(methoxymethoxy)-2-vinylcyclopentanecarboxylate 305**

A 5-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (1 mL) and compound 304 (0.09 g, 0.2 mmol, in 0.5 mL of tetrahydrofuran) in order. After the
solution was cooled to 0 °C in the ice bath, TBAF (1.0 M in tetrahydrofuran. 0.4 mL,
0.4 mmol,) was added in one portion. After TLC analysis (hexane: ethyl acetate = 4:1;
Rf = 0.30) indicated that the starting material was consumed, the solution was
quenched by cautious addition of saturated aqueous ammonium chloride (1 mL). The
mixture was extracted with diethyl ether (3 x 5 mL). The combined organic layers
were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The
resulting liquid was filtered and concentrated under reduced pressure. The product
was purified by flash chromatography on silica ((hexanes:ethyl acetate = 12:1, Rf =
0.30) to offer 36 mg (80%) of 305 as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ
5.82 (m, 1H), 5.04 (dd, 1H, J = 0.8, 15.5 Hz), 4.98 (dd, 1H, J = 1.1, 10.1 Hz), 4.62 (s,
2H), 4.23 (m, 1H), 4.14 (m, 2H), 3.36 (s, 3H), 2.75-2.69 (m, 2H), 2.30 (m, 1H), 2.05
(m, 2H), 1.71 (m, 1H), 1.24 (t, 3H, J = 7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 176.4,
141.7, 115.8, 96.5, 69.2, 61.7, 56.6, 49.5, 47.6, 40.7, 38.2, 15.5.

(1R,2R,4R)-Ethyl
4-(methoxymethoxy)-2-((1R)-1-(p-tolysulfanyl)-2-(trimethylsilyl)ethyl)cyclopentancarboxylate 308

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of
nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (3 mL),
and diisopropylamine (0.1 mL, 0.75 mmol) in order. After the solution was cooled to
0 °C, n-BuLi (2.0 M in hexanes, 0.37 mL, 0.75 mmol) was added in one portion. After
stirring for 10 min, the reaction mixture was cooled to -78 °C using dry ice in acetone, compound 307 (0.06 g, 0.25 mmol, in 0.5 mL of THF) was added. After the solution was allowed to stir for 15 min, compound 294 (0.09 g, 0.33 mmol, in 0.33 mL of THF) was added in one portion. The solution was allowed to stir for 15 min at -78 °C and then warm to 0 °C. After TLC analysis (hexanes:ethyl acetate = 3:1; Rf = 0.20) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (2 mL). The mixture was extracted with diethyl ether (3 x 5 mL), washed with brine (5 mL). The combined organic layers were dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexane: ethyl acetate = 3:1, Rf = 0.15) to offer 88 mg (80%) of 308 as a colorless liquid. [α]25 D = -52 (c = 0.003 g/mL, THF). 1H NMR (400 MHz, CDC13 ) δ 7.60-7.58 (d, 2H, J = 8.0 Hz), 7.50-7.48 (d, 2H, J = 8.0 Hz), 4.91-4.84 (dd, 2H, J = 6.9, 25.3 Hz), 4.44 (m, 1H), 4.41-4.37 (q, 2H, J = 7.1, Hz), 3.66-3.54 (m, 2H), 3.58 (s, 3H), 3.02 (m, 1H), 2.69 (m, 1H), 2.60 (s, 3H), 2.60-2.34 (m, 3H), 1.52-1.49 (t, 3H, J = 7.1 Hz), 0.99-0.97 (m, 2H), 0.20 (s, 9H); 13C NMR (100 MHz, CDC13 ) δ 176.2, 141.8, 141.8, 131.0, 125.4, 96.4, 77.1, 66.8, 62.2, 56.9, 47.4, 47.0, 37.9, 35.0, 22.7, 15.8, 10.6, 0.0. IR (neat, cm⁻¹): 2964, 2882, 1727, 1614, 1596.
(1R,2S,4S)-Ethyl 4-(methoxymethoxy)-2-vinylcyclopentanecarboxylate 309

A 25-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (5 mL) and compound 308 (0.09 g, 2 mmol, in 2 mL of tetrahydrofuran) in order. After the solution was cooled to 0 °C in the ice bath, TBAF (1.0 M in tetrahydrofuran, 3.0 mL, 3.0 mmol) was added in one portion. After TLC analysis (hexanes:ethyl acetate = 3:1; Rf = 0.15) indicated that the starting material was consumed, the solution was quenched by cautious addition of saturated aqueous ammonium chloride (3 mL). The mixture was extracted with diethyl ether (2 x 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 10:1, Rf = 0.25) to offer 0.39 g (85%) of 309 as a colorless liquid. 1H NMR (400 MHz, CDCl3) δ 5.80 (m, 1H), 5.04 (dd, 1H, J = 0.9, 16.4 Hz), 4.98 (dd, 1H, J = 1.0, 10.1 Hz), 4.62 (s, 2H), 4.23 (m, 1H), 4.18-4.10 (m, 2H), 3.36 (s, 3H), 2.76-2.68 (m, 2H), 2.30 (m, 1H), 2.08-2.02 (m, 2H), 1.58 (m, 1H), 1.26-1.23 (t, 3H, J = 7.1 Hz); 13C NMR (100 MHz, CDCl3) δ 175.3, 140.6, 114.8, 95.5, 66.1, 60.6, 55.6, 48.4, 46.6, 39.7, 37.2, 14.5.

((1R,2S,4S)-4-(Methoxymethoxy)-2-vinylcyclopentyl)methanol 310

A 10-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with tetrahydrofuran (3 mL),
lithium aluminum hydride (15 mg, 0.4 mmol) and compound 309 (18 mg, 0.075 mmol) in the indicated order. The solution was refluxed till TLC analysis (hexanes:ethyl acetate = 3:1; \( R_f = 0.20 \)) indicated that the starting material was consumed. The solution was cooled to room temperature and quenched by cautious and sequential addition of water (1 mL), 10% aqueous sodium hydroxide (1 mL), and water (3 mL). After stirred for 10 min, the solution was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1, \( R_f = 0.10 \)) to offer 7 mg (50%) 310 as a colorless liquid.

\[ ^1H\text{ NMR (500 MHz, CDCl}_3\] \( \delta \) 5.82 (m, 1H), 5.04 (dd, 1H, \( J = 1.0, 17.1 \text{ Hz} \)), 4.96 (dd, 1H, \( J = 1.7, 10.1 \text{ Hz} \)), 4.63 (s, 2H), 4.16 (m, 1H), 3.68 (dd, 1H, \( J = 5.4, 10.8 \text{ Hz} \)), 3.54 (dd, 1H, \( J = 6.1, 10.8 \text{ Hz} \)), 3.36 (s, 3H), 2.27-2.18 (m, 3H), 2.05 (m, 1H), 1.92 (m, 1H), 1.67 (m, 1H), 1.56 (m, 1H); \[ ^13C\text{ NMR (100 MHz, CDCl}_3\] \( \delta \) 142.5, 114.5, 95.5, 76.9, 65.7, 55.5, 46.0, 45.8, 40.4, 36.2.

(S)-Hept-6-en-2-yl acetate 313

A 100-mL oven-dried, round-bottomed flask, equipped with a septum with a flow of nitrogen through a needle and a stir bar, was charged with \( \text{Mg}^\circ \) (0.6 g, 25 mmol), THF (30 mL) and a crystal of iodine. 4-Bromo-1-butene (1.3 mL, 13 mmol) was dissolved in tetrahydrofuran (10 mL). A portion of the bromobutene solution (1 mL) was added and the mixture was allowed to stir until the brown color of the mixture disappeared. The solution was allowed to stir for an additional 10 min, then
4-bromo-1-butene solution was added dropwise over a 1-hour period using a syringe pump. The mixture was allowed to stir for an additional 1 h and was brought to -40 °C and copper(I) iodide (50 mg, 0.26 mmol) was added. The resulting light green mixture was allowed to stir for an additional 10 minutes, at which time (S)-propylene oxide (0.35 mL, 5 mmol) was added in a single portion. The mixture was allowed to warm to -15 °C and allowed to stir for an additional 2.5 hours, then quenched with saturated aqueous ammonium chloride (10 mL). The layers were separated and the organic layer was washed with H$_2$O (10 mL) and brine (10 mL). The layers were separated and the combined aqueous layers were extracted with diethyl ether (3 x 50 mL) and the combined organic layers were dried over anhydrous sodium sulfate. The solution was filtered and concentrated under reduced pressure. The resulting crude residue was dissolved in a 25-mL oven-dried round-bottomed flask with 8 mL diethyl ether. Acetyl chloride (0.71 mL, 10 mmol, freshly distilled) was added to the solution followed with addition of pyridine (0.80 mL, 10 mmol). The solution was allowed to reflux till TLC analysis (hexane: ethyl acetate = 3:1; $R_f = 0.10$) indicated that the starting material was consumed. After cooling to the room temperature, the solution was washed with 1M HCl (3 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica (hexanes:ethyl acetate = 15:1, $R_f = 0.15$) to yield 0.66 g (85%) of 313 as a colorless liquid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.71 (m, 1H), 4.93 (dd, 1H, $J = 1.7, 17.1$ Hz), 4.88 (dd, 1H, $J = 0.9, 11.2$ Hz), 4.83 (m, 1H), 2.01-1.96.
(\text{m,} 2\text{H}), \ 1.95 \ (\text{s,} \ 3\text{H}), \ 1.56-1.18 \ (\text{m,} \ 4\text{H}), \ 1.14 \ (\text{d,} \ 3\text{H}, \ J = 6.3 \ \text{Hz}); \ ^{13}\text{C NMR} \ (125 \ \text{MHz,} \ \text{CDCl}_3) \ \delta \ 169.7, \ 137.4, \ 113.7, \ 69.8, \ 34.3, \ 32.5, \ 23.7, \ 20.2, \ 18.9.

\textit{(6S,11aS,13S,14aR,E)-13-(Methoxymethoxy)-6-methyl-2,3,6,7,8,9,12,13,14,14a-decahydro-1H-cyclopenta[f][1]oxacyclotridecene-1,4(11aH)-dione 314}

A 10-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 3 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 1.0 mL, 1.0 mmol). The solution was cooled to 0 °C and compound 294A (62 mg, 0.2 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, methylene iodide (0.08 mL, 1.0 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 hour at room temperature. Diethyl zinc (1.0 M in hexanes, 0.5 mL, 0.5 mmol) was added to the solution at room temperature and after 10 minutes, methylene iodide (0.04 mL, 0.5 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (2 mL). The mixture was extracted with diethyl ether (3 x 5 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate =7:1; \ R_f = 0.20) to offer 49 mg (75%) of 314 as a colorless liquid. \ ^1\text{H NMR} \ (500 \ \text{MHz,} \ \text{CDCl}_3) \ \delta \ 5.56 \ (\text{ddd}, \ 1\text{H}, \ J = 5.0, \ 10.0, \ 15.0 \ \text{Hz}), \ 5.31 \ (\text{dd}, \ 1\text{H}, \ J = 8.8,
15.2 Hz), 4.78 (m, 1H), 4.62 (s, 2H), 4.21 (m, 1H), 3.36 (s, 3H), 3.01-2.91 (m, 2H), 2.80 (m, 1H), 2.66-2.54 (m, 2H), 2.39-2.28 (m, 2H), 2.05-1.81 (m, 4H), 1.64-1.46 (m, 2H), 1.28-1.10 (m, 3H), 1.19 (d, 3H, J = 6.3 Hz); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 210.9, 172.9, 133.2, 132.2, 95.5, 71.8, 56.6, 55.6, 46.7, 40.3, 38.8, 36.6, 32.6, 31.1, 29.5, 24.2, 19.6.

e) Preparation of β-Substituted-γ-Keto Carbonyl Compounds

Methyl 3-methyl-4-oxopentanoate 346A

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 8 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C and 347A (58 mg, 0.5 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, 1,1-diiodoethane (0.25 mL, 2.5 mmol) was added dropwise by syringe. The mixture was stirred for 1 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (3 x 8 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1; \(R_f\) = 0.3) to offer 55 mg (76%) of 346A as a colorless liquid. \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.64 (s, 3H), 2.99 (m, 1H), 2.74 (dd, 1H, J = 8.6, 16.7 Hz), 2.28
(dd, 1H, J = 5.5, 16.8 Hz), 2.20 (s, 3H), 1.14 (d, 3H, J = 7.3 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 210.7, 172.7, 51.7, 42.7, 36.6, 28.4, 16.5. IR (neat, cm$^{-1}$): 2955, 1737, 1716, 1437.

**Methyl 3,5,5-trimethyl-4-oxohexanoate 346B**

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 8 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C and compound 347B (79 mg, 0.5 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, 1,1-diiodoethane (0.25 mL, 2.5 mmol) was added dropwise by syringe. The mixture was stirred for 1 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (3 x 8 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1; $R_f = 0.64$) to offer 76 mg (82%) of 346B as a colorless liquid. $^1$H NMR (500 MHz, CDCl$_3$) δ 3.61 (s, 3H), 3.43 (m, 1H), 2.66 (dd, 1H, J = 8.0, 16.4 Hz), 2.28 (dd, 1H, J = 6.3, 16.4 Hz), 1.16 (s, 9H), 1.05 (d, 3H, J = 7.0 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 218.1, 172.5, 51.5, 44.5, 38.1, 36.2, 26.5, 18.3. IR (neat, cm$^{-1}$): 2972-2956, 1740, 1703, 1480, 1437.
Ethyl 3-methyl-4-oxo-4-phenylbutanoate 346C

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 8 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C and compound 347C (96 mg, 0.5 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, 1,1-diodoethane (0.25 mL, 2.5 mmol) was added dropwise by syringe. The mixture was stirred for 1 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (3 x 8 mL). The combined organic extracts were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1; Rf = 0.52) to offer 92 mg (84%) of 346C as a colorless liquid. 1H NMR (500 MHz, CDCl3) δ 7.98-7.96 (m, 2H), 7.54 (m, 1H), 7.47-7.44 (m, 2H), 4.08 (q, 2H, J = 7.1 Hz), 3.94 (m, 1H), 2.94 (dd, 1H, J = 8.5, 16.7 Hz), 2.44 (dd, 1H, J = 5.7, 16.7 Hz), 1.20 (t, 3H, J = 7.3 Hz), 1.18 (d, 3H, J = 7.1 Hz); 13C NMR (125 MHz, CDCl3) δ 202.7, 172.2, 135.9, 133.0, 128.6, 128.3, 60.5, 37.5, 37.1, 17.7, 14.0. IR (neat, cm⁻¹): 2979, 1733, 1683, 1448, 1377.
Benzyl 3-methyl-4-oxopentanoate 346D

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 8 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C and compound 347D (96 mg, 0.5 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, 1,1-diiodoethane (0.25 mL, 2.5 mmol) was added dropwise by syringe. The mixture was stirred for 1 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (3 x 8 mL). The combined organic extracts washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1; Rf = 0.30) to offer 88 mg (80%) of 346D as a colorless liquid. ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.30 (m, 5H), 5.11-5.08 (d, 2H, J = 4.7 Hz), 3.03 (m, 1H), 2.82 (dd, 1H, J = 8.7, 16.8 Hz), 2.34 (dd, 1H, J = 5.4, 16.8 Hz), 2.20 (s, 3H), 1.15 (d, 3H, J = 7.3 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 210.6, 172.1, 135.8, 128.5, 128.2, 128.1, 66.4, 42.7, 36.8, 28.3, 16.5. IR (neat, cm⁻¹): 2969-2934, 1734, 1715, 1456.

 tert-Butyl 3-methyl-4-oxopentanoate 346E

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 8 mL of methylene
chloride and diethyl zinc (1.0 M in hexanes, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C and compound 347E (79 mg, 0.5 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, 1,1-diiodoethane (0.25 mL, 2.5 mmol) was added dropwise by syringe. The mixture was stirred for 1 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (3 x 8 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexane: ethyl acetate = 7:1; Rf = 0.50) to offer 82 mg (88%) of 346E as a colorless liquid. ¹H NMR (500 MHz, CDCl₃) δ 2.95 (m, 1H), 2.66 (dd, 1H, J = 8.6, 16.5 Hz), 2.23 (dd, 1H, J = 5.5, 16.5 Hz), 2.21 (s, 3H), 1.43 (s, 9H), 1.13 (d, 3H, J = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 210.8, 171.4, 80.6, 42.9, 38.2, 28.3, 28.0, 16.3. IR (neat, cm⁻¹): 2977-2934, 1727, 1717, 1367.

**Allyl 3-methyl-4-oxopentanoate 349**

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 8 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 1.5 mL, 1.5 mmol). The solution was cooled to 0 °C and compound 348 (73 mg, 0.5 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, 1,1-diiodoethane (0.15 mL,
1.5 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 hour at room temperature. Diethyl zinc (1.0 M in hexanes, 1.5 mL, 1.5 mmol) was added to the solution at room temperature and after 10 minutes, 1,1-diiodoethane (0.15 mL, 1.5 mmol) was added dropwise by syringe. The mixture was stirred for 0.5 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (3 x 8 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1; Rf = 0.37) to offer 63 mg (74%) of 349 as a colorless liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.89 (m, 1H), 5.30 (dd, 1H, \(J = 1.5, 17.2\) Hz), 5.22 (dd, 1H, \(J = 1.3, 10.4\) Hz), 4.57-4.54 (m, 2H), 3.01 (m, 1H), 2.79 (dd, 1H, \(J = 8.7, 16.8\) Hz), 2.32 (dd, 1H, \(J = 5.4, 16.8\) Hz), 2.21 (s, 3H), 1.15 (d, 3H, \(J = 7.2\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 210.6, 171.9, 132.0, 118.3, 65.2, 42.7, 36.8, 28.4, 16.5. IR (neat, cm\(^{-1}\)): 3021-2936, 1733, 1716, 1460.

**Methyl 4-oxo-3-phenylpentanoate 357A**

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 8 mL of methylene chloride and diethyl zinc (1.0 M in hexane, 2.5 mL, 2.5 mmol). The solution was cooled to 0 °C and compound 347A (58 mg, 0.5 mmol, in 1 mL of methylene chloride)
was added to the solution. After stirring for 10 minutes, 1,1-diiodotoluene (0.86 g, 2.5 mmol, in 2 mL of methylene chloride) was added dropwise by syringe. The mixture was stirred for 1 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (3 x 8 mL). The combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1; R_f = 0.40) to offer 76 mg (74%) of 357A as a colorless liquid. \(^1\)H NMR (400 MHz, CDCl₃) δ 7.36-7.20 (m, 5H), 4.19 (dd, 1H, J = 5.0, 9.8 Hz), 3.65 (s, 3H), 3.22 (dd, 1H, J = 9.9, 17.0 Hz), 2.53 (dd, 1H, J = 5.0, 17.0 Hz), 2.12 (s, 3H); \(^1^3\)C NMR (100 MHz, CDCl₃) δ 206.8, 172.5, 137.3, 129.2, 128.2, 127.7, 54.8, 51.8, 36.7, 28.8. IR (neat, cm\(^{-1}\)): 3028, 2953-2922, 1754, 1736, 1716, 1453, 1437.

**tert-Butyl 4-oxo-3-phenylpentanoate 357B**

A 25-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 8 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 2.0 mL, 2.0 mmol). The solution was cooled to 0 °C and compound 347B (63 mg, 0.4 mmol, in 1 mL of methylene chloride) were added to the solution. After stirring for 10 minutes, 1,1-diiodotoluene (0.69 g, 2.0 mmol, in 2 mL of methylene chloride) was added dropwise by syringe. The

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mixture was stirred for 1 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with diethyl ether (3 x 8 mL). The combined organic extracts were washed with brine (5 mL), and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 7:1; Rf = 0.64) to offer 44 mg (44%) of 357B as a colorless liquid. $^1$H NMR (500 MHz, CDCl₃) ð 7.34-7.20 (m, 5H), 4.12 (dd, 1H, J = 5.3, 9.6 Hz), 3.11 (dd, 1H, J = 9.8, 16.7 Hz), 2.46 (dd, 1H, J = 5.3, 16.7 Hz), 2.11 (s, 3H), 1.39 (s, 9H); $^{13}$C NMR (100 MHz, CDCl₃) ð 206.9, 171.3, 137.5, 129.0, 128.3, 127.6, 80.7, 55.0, 38.2, 28.9, 28.0. IR (neat, cm⁻¹): 2978-2930, 1719, 1367, 1355.

(S)-1-(4-Benzyl-2-oxooxazolidin-3-yl)-3-methylpentane-1,4-dione 366A and 366B

A 10-mL oven-dried, round-bottomed flask equipped with a stir bar and a septum with a flow of nitrogen through a needle was charged with 3 mL of methylene chloride and diethyl zinc (1.0 M in hexanes, 1.25 mL, 1.25 mmol). The solution was cooled to 0 °C and compound 365 (65 mg, 0.25 mmol, in 1 mL of methylene chloride) was added to the solution. After stirring for 10 minutes, 1,1-diiodoethane (0.13 mL, 1.25 mmol) was added dropwise by syringe. The mixture was stirred for 1 hour at room temperature and quenched by cautious addition of saturated aqueous ammonium chloride (2 mL). The mixture was extracted with diethyl ether (3 x 5 mL). The
combined organic extracts were washed with brine (5 mL) and dried over anhydrous sodium sulfate. The resulting liquid was filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica (hexanes:ethyl acetate = 3:1; R$_f$ = 0.20) to offer 36 mg (50%) of mixture of 366A (24%) and 366B (26%) as a colorless liquid. 366A: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35-7.20 (m, 5H), 4.64 (m, 1H), 4.22-6.16 (m, 2H), 3.50 (dd, 1H, $J = 9.8, 18.3$ Hz), 3.20 (dd, 1H, $J = 3.3, 13.5$ Hz), 3.12 (m, 1H), 2.84 (dd, 1H, $J = 3.9, 18.2$ Hz), 2.80 (dd, 1H, $J = 8.5, 12.9$ Hz), 2.28 (s, 3H), 1.22 (d, 3H, $J = 7.4$ Hz); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 211.1, 172.2, 153.7, 135.3, 129.7, 129.2, 127.5, 66.4, 55.1, 42.3, 39.0, 37.9, 28.7, 16.8. 366B: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.34-7.18 (m, 5H), 4.62 (m, 1H), 4.22 (dd, 1H, $J = 9.1, 9.1$ Hz), 4.15 (dd, 1H, $J = 2.6, 9.1$ Hz), 3.43 (dd, 1H, $J = 10.3, 18.4$ Hz), 3.27 (dd, 1H, $J = 3.4, 13.4$ Hz), 3.15 (m, 1H), 2.91 (dd, 1H, $J = 3.6, 18.4$ Hz), 2.74 (dd, 1H, $J = 9.8, 13.4$ Hz), 2.28 (s, 3H), 1.22 (d, 3H, $J = 7.3$ Hz); $^{13}$C (100 MHz, CDCl$_3$) $\delta$ 211.4, 172.1, 153.7, 135.4, 129.6, 129.2, 127.6, 66.5, 55.4, 42.1, 39.0, 38.1, 29.9, 16.8.
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